TALAR CARTILAGE DEFORMATION FOLLOWING STATIC AND DYNAMIC LOADING IN THOSE WITH AND WITHOUT CHRONIC ANKLE INSTABILITY

Kyeongtak Song

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Approved by:

Erik A. Wikstrom

Brian G. Pietrosimone

J. Troy Blackburn

Darin A. Padua

Joshua N. Tennant

ABSTRACT

Kyeongtak Song: Talar Cartilage Deformation Following Static and Dynamic Loading
in Those With and Without Chronic Ankle Instability
(Under the direction of Erik A. Wikstrom)

Chronic ankle instability (CAI) has been linked with the development of ankle post-traumatic osteoarthritis. To date, compositional changes have been noted using advanced MR-based imaging techniques which are not clinically accessible or cost-effective. Ultrasonography (US) is a valid and reliable technique to assess cartilage thickness, but it remains unknown if CAI influences the magnitude of cartilage deformation relative to uninjured healthy controls during static and/or dynamic loading. Therefore, the purpose of this study was to establish the acute response of talar cartilage to a standardized static and dynamic loading protocol in individuals with CAI compared to uninjured healthy controls. Also, the aims of this study to identify patient-, clinician, and laboratory-oriented correlates of talar cartilage thickness (at rest) and deformation in those with CAI.

Thirty CAI and 30 uninjured controls completed the patient-, clinician-, and laboratory-oriented assessment during the first session. In the second and third sessions, participants completed the US assessments before and after static and dynamic loading protocol based on the counterbalanced order of testing sessions. Normalized cross-sectional area of the medial, lateral, and overall talar cartilage and percentage change scores were calculated.

The results from this study indicate that a greater magnitude of talar cartilage deformation occurred after static and dynamic loading in those with CAI compared to healthy individuals. In those with CAI, altered ankle biomechanics and increased vertical ground

reaction force components during a single leg hop were correlated with increased cartilage deformation after a dynamic loading protocol. Similarly, decreased dorsiflexion range of motion and worse performance on the side hop test were correlated with greater cartilage deformation in those with CAI. Also, our data illustrates relationships among inversion laxity and poor static postural control with increased talar cartilage deformation following a static loading protocol.

Our results suggest that US is capable to detecting differences in cartilage behavior between those with CAI and uninjured controls following standardized physiologic loads. These results may also provide to better understanding the factors contributing to altered cartilage behavior in response to static and dynamic loads in those with CAI and may represent targets for future therapeutic interventions.

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LIST OF ABBREVIATIONS

ATFL Anterior Talofibular Ligament

CAI Chronic Ankle Instability

FAAM Foot and Ankle Ability Measure

IdFAI Identification of functional ankle instability

LAS Lateral Ankle Sprain

MR Magnetic Resonance

OA Osteoarthritis

OCD Osteochondritis dissecans

PTOA Post-Traumatic Osteoarthritis

SEBT Star Excursion Balance Test

US Ultrasound

VGRF Vertical Ground Reaction Force

CHAPTER 1: INTRODUCTION

Lower extremity injury is a leading cause for the cessation of physical activity participation.[1] Decreased physical activity results in decreased quality of life, and significant long-term negative sequelae.[2] Ankle sprains are the most common musculoskeletal injury associated with physical activity and athletic participation, accounting for approximately 60% of all injuries that occur during interscholastic and intercollegiate sports.[3, 4] Up to 75% of individuals who sprain their ankle subsequently develop chronic ankle instability (CAI); a condition characterized by life-long residual symptoms, recurrent injury, and decreased physical activity.[5-7] Further, as many as 78% of those with CAI develop ankle post-traumatic osteoarthritis (PTOA).[8, 9] Just a single lateral ankle sprain causes talar degeneration in human[10] and has been demonstrated to reduce knee joint space in an animal model.[11]

The exact mechanisms of how ankle sprains and CAI contribute to the development of PTOA throughout the lower extremity is unknown. However, sensorimotor,[12] structural,[13, 14] and biomechanical[15-19] alterations likely increase joint contact strain and lead to degenerative changes.[8, 9, 20] For example, Bischof et al[21] found that the talar peak contact strain translated anteriorly and medially with increasing weight acceptance in the involved ankle of those with unilateral CAI. Similarly, Bae et al[22] found that talar cartilage strain was increased while walking in those with a history of ankle injury. Golditz et al[23] also showed that longer time to stabilization after a single leg jump landing correlated with worse lateral talar cartilage composition in those with CAI. Our own data demonstrate: 1) that thinner talar cartilage thickness, measured via ultrasonography, correlates with the increased vGRF loading rates during walking gait in those with CAI[24] and 2) postural instability correlates with declines in cartilage composition (T1rho).[25] These results suggest that sensorimotor dysfunction and/or biomechanical alterations represent plausible mechanisms for declines in cartilage health in those with CAI. Fully elucidating the underlying mechanisms responsible for cartilage health declines in those with CAI is crucial for refining intervention strategies that athletic trainers can use to slow the progression of PTOA following lateral ankle sprains.

No effective PTOA treatment exists, particularly once joint disease becomes severe. Thus, the most promising approach for slowing PTOA progression is early interventions that address the sensorimotor[12] and biomechanical alterations[15-19] caused by lateral ankle sprains. Unfortunately, quantifying early joint degeneration is limited to magnetic resonance (MR) techniques which are costly and do not allow an athletic trainer to evaluate an intervention's ability to slow early PTOA progression in the clinical setting. A hallmark feature of PTOA is a decline in articular cartilage health[26] but the earliest deleterious changes in cartilage health involve alterations in cartilage composition (e.g. reduced proteoglycan density, collagen disorganization) without overt changes in cartilage morphology (e.g. thickness).[27] Using MR, T2 mapping showed compositional changes in young athletes that had functional ankle instability for <5 years.[28] Our data also show compositional declines (i.e. decreased proteoglycan density via T1rho MR scans) in college-aged CAI patients relative to controls.[29] Despite compositional differences, talar cartilage volume did not differ between the groups. These compositional changes are theorized to alter the ability of the cartilage to respond to loading.[30] Compositional breakdown is also purported to impair the resiliency (i.e. recovery from loading) of the cartilage.[31] Thus, acute cartilage deformation and resiliency from physical activity may represent a surrogate of cartilage composition, as deformation and resiliency are governed by tissue composition.[32]

Previous MR studies indicate that talar cartilage volume decreases after static (single leg standing, double limb squat, single limb squat) and dynamic loading (single leg drop jump, single limb hopping).[33] However, we do not know if the observed deformation patterns are normal as an uninjured control group was not assessed. Our knowledge of cartilage recovery in CAI patients is also based on MR technology and the load from which the cartilage was recovering, was not controlled for.[28, 34] While MR remains the gold standard in cartilage visualization, it is too expensive and time intensive to be useful as a clinical screening tool for poor cartilage health. Ultrasonography (US), is a valid and reliable technique to assess cartilage thickness at the knee[35-37] and our data showed that US talar cartilage thickness was correlated with MR volume. Thus, US may represent a viable alternative to MR. However, it remains unknown if CAI influences the magnitude of cartilage deformation and/or resiliency relative to uninjured healthy controls during static and/or dynamic loading.

Our long-term goal is to develop therapeutic interventions that can slow PTOA progression in those with a history of lateral ankle sprains and CAI. The first step to achieving this goal, is establishing sound and cost-effective experimental protocols capable of quantifying ankle cartilage health. Therefore, the purpose of this study will be to establish the acute response of talar and femoral cartilage to a standardized static and dynamic loading protocol in individuals with CAI compared to uninjured healthy controls. To achieve this purpose, we propose the following specific aims:

Primary Aims

Specific Aim 1: To determine if talar cartilage deformation using ultrasonography following standardized standing and hopping protocols differs between those with CAI and healthy controls.

Research Questions

1.1. Do individuals with CAI demonstrate different talar cartilage deformation following a 2-minute standing protocol compared to healthy controls?

1.2. Do individuals with CAI demonstrate different talar cartilage deformation following a 60-hop protocol compared to healthy controls?

Hypotheses

1.1. CAI group will demonstrate greater talar cartilage deformation following a 2-minute standing protocol relative to healthy controls.

1.2. CAI group will demonstrate greater talar cartilage deformation following a 60-hop protocol relative to control group.

Specific Aim 2: To identify patient and clinician-oriented correlates of talar cartilage thickness (at rest) and deformation in those with CAI.

Research Questions

2.1.1 Does self-reported function correlate with talar cartilage thickness at rest?

2.1.2 Does self-reported function correlate with talar cartilage deformation after a standing protocol?

2.1.3 Does self-reported function correlate with talar cartilage deformation after a hopping protocol?

2.2.1. Do dorsiflexion range of motion and dynamic postural control correlate with talar cartilage thickness at rest?

2.2.2. Do dorsiflexion range of motion and dynamic postural control correlate with talar cartilage deformation after a standing protocol?

2.2.3. Do dorsiflexion range of motion and dynamic postural control correlate with talar cartilage deformation after a hopping protocol?

2.3.1. Does functional hop performance correlate with talar cartilage deformation after a standing protocol?

2.3.2. Does functional hop performance correlate with talar cartilage deformation after a hopping protocol?

Hypotheses

2.1.1. Lower Foot and Ankle Ability Measure (FAAM), the FAAM-Sport (FAAM-S), and the Foot and Ankle Osteoarthritis Scale (FAOS) scores will correlate with thinner talar cartilage thickness at rest.

2.1.2. Lower FAAM, FAAM-S, and FAOS scores will correlate with increased talar cartilage deformation after a standing protocol.

2.1.3. Lower FAAM, FAAM-S, and FAOS scores will correlate with increased talar cartilage deformation after a hopping protocol.

2.2.1. Shorter distances during the weight-bearing lunge test and reach distances during star excursion balance test will correlate with thinner talar cartilage thickness at rest.

2.2.2. Shorter distances during the weight-bearing lunge test and reach distances during star excursion balance test will correlate with increased talar cartilage deformation after a standing protocol.

2.2.3. Shorter distances during the weight-bearing lunge test and reach distances during star excursion balance test will correlate with increased talar cartilage deformation after a hopping protocol.

2.3.1. Shorter times and longer distances during functional hop tasks will correlate with decreased talar cartilage deformation after a standing protocol.

2.3.2. Shorter times and longer distances during functional hop tasks will correlate with decreased talar cartilage deformation after a hopping protocol.

Specific Aim 3: To identify laboratory-oriented correlates (i.e. biomechanical and sensorimotor outcomes) of talar cartilage thickness (at rest) and deformation in those with CAI.

Research Questions

3.1.1. Does ankle joint laxity correlate with talar cartilage thickness at rest?

3.1.2. Does ankle joint laxity correlate with talar cartilage deformation following a standing protocol?

3.1.2. Does ankle joint laxity correlate with talar cartilage deformation following a hopping protocol?

3.2.1. Does instrumented static postural control correlate with talar cartilage thickness at rest?

3.2.2. Does instrumented static postural control correlate with talar cartilage deformation following a standing protocol?

3.2.3. Does instrumented static postural control correlate with talar cartilage deformation following a hopping protocol?

3.3.1. Do ankle kinematics at initial contact during walking gait, hopping, and jump landing correlate with talar cartilage thickness at rest?

3.3.2. Do ankle kinematics at initial contact during standing and walking gait correlate with talar cartilage deformation after a standing protocol?

3.3.3. Do ankle kinematics during hopping and jump landing correlate with talar cartilage deformation after a hopping protocol?

3.3.4. Do kinetic variables during the loading phase of standing and walking correlate with talar cartilage deformation after a standing protocol?

3.3.5. Do kinetic variables during the loading phase of hopping and jump landing correlate with talar cartilage deformation after a hopping protocol?

Hypotheses

3.1.1. Increased anterior-posterior and inversion-eversion joint laxity using ankle arthrometer will correlate with thinner talar cartilage thickness at rest.

3.1.2. Increased anterior-posterior and inversion-eversion joint laxity using ankle arthrometer will correlate with increased talar cartilage deformation after standing protocol.

3.1.3. Increased anterior-posterior and inversion-eversion joint laxity using ankle arthrometer will correlate with increased talar cartilage deformation after hopping protocol.

3.2.1. Increased center of pressure outcomes during 10-s single limb stance will correlate with thinner talar cartilage thickness at rest.

3.2.2. Increased center of pressure outcomes during 10-s single limb stance will correlate with increased talar cartilage deformation after standing protocol.

3.2.3. Increased center of pressure outcomes during 10-s single limb stance will correlate with increased talar cartilage deformation after hopping protocol.

3.3.1. Increased ankle joint angles at the initial contact during walking, hopping, and jump landing will correlated with thinner talar cartilage thickness at rest.

3.3.2. Increased ankle joint range suring single limb standing and ankle joint angle at the initial contact during walking will correlate with increased talar cartilage deformation after a standing protocol.

3.3.3. Increased ankle joint angles at the initial contact during hopping and jump landing will correlate with increased talar cartilage deformation after a hopping protocol.

3.3.4. Higher peak vertical ground reaction forces and loading rate during the loading phase of single limb standing and walking will correlate with increased talar cartilage deformation after a standing protocol.

3.3.5. Higher peak vertical ground reaction forces and loading rates during the loading phase of hopping and jump landing will correlate with increased talar cartilage deformation after a hopping protocol.

Secondary Research Questions to be addressed

These questions will be addressed, but not as part of formal dissertation.

SRQ 1: To determine the time needed for talar cartilage to reach a resting state (i.e. fully recovery from real world activity).

SRQ 2: To determine if cumulative external loading during a one-week monitoring period correlates to talar cartilage deformation.

Research Question

2.1. Do average steps-per-day and minutes of moderate-to-vigorous physical activity during a one-week monitoring period correlate to talar cartilage deformation following standing protocol?

2.2. Do average steps-per-day and minutes of moderate-to-vigorous physical activity during a one-week monitoring period correlate to talar cartilage deformation following hopping protocol?

SRQ 3: To determine if cumulative external loading during a one-week monitoring period correlates to talar cartilage recovery during a 60-minute off-loading period.

SRQ4: To determine if femoral cartilage deformation using ultrasonography following a standardized standing and hopping protocols differs between those with CAI and healthy controls.

Research Questions

4.1. Do individuals with CAI demonstrate different femoral cartilage deformation following a standing protocol compared to healthy controls?

4.2. Do individuals with CAI demonstrate different femoral cartilage deformation following a hopping protocol compared to healthy controls?

SRQ5: To identify patient, clinician, and laboratory-oriented correlates to femoral cartilage thickness (at rest) and deformation in those with CAI.

Research Questions

5.1. Does self-reported function correlate with femoral cartilage thickness at rest and deformation after loading protocols?

5.2. Do clinician-oriented outcomes (i.e. range of motion, star excursion balance test, functional hop tests) correlate with femoral cartilage thickness at rest and deformation after loading protocols?

5.3. Do biomechanical outcomes (i.e. instrumented static balance, kinematics and kinetics) during standing, walking gait, hopping, and jump landing correlate with femoral cartilage thickness at rest and deformation following loading protocols?

CHAPTER 2: REVIEW OF LITERATURE

Plausible Mechanisms of and Techniques to Assess Ankle Joint Degeneration following Lateral Ankle Sprains: A Narrative Review

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1. Introduction

Lateral ankle sprain (LAS) is the most common lower extremity musculoskeletal injury in physically active persons[4, 38, 39] and the general population.[40-42] LASs are commonly considered a benign injury and <50% of individuals with LAS seek formal treatment from health care providers.[43] However, up to 70% of patients with LASs experience lingering problems including recurrent ankle sprains, residual symptoms, decreased function, and activity restrictions. These consequences represent the hallmark characteristics of chronic ankle instability (CAI).[44-46] While the consequences of CAI development following LASs are well established, the causes for CAI development have not been clearly determined. The current theory, highlights a cascade of events (i.e. maladaptive strategies) that start with ligamentous trauma and deafferentation and result in altered spinal and supraspinal levels of motor control program.[47] The culmination of these cascades appears to be clinical manifestations such as recurrent sprains and giving way episodes. These impairments following ankle sprains may contribute to aberrant biomechanics. Combined, these appear to directly or indirectly play a role in talar cartilage degeneration.

Ankle joint osteoarthritis (OA) causes significant physical limitations to an individual.[48] Roughly 12% of symptomatic OA is attributable to lower extremity post-traumatic OA (PTOA), and up to 80% of all cases of ankle OA is post-traumatic in nature.[49-51] PTOA develops secondary to joint trauma. Common etiologies for ankle PTOA are a history of both a single ankle sprain and recurrent ankle sprains.[49, 51, 52] Specifically, Saltzman et al.[49] reported that 13.7% and 14.6% of all cases of ankle PTOA were the result of a single ankle sprain and recurrent ankle sprains, respectively. Harrington et al.[52] reported that about 80% of those with CAI beyond 10 years had degenerative changes of the talar articular cartilage. More importantly, patients with ankle PTOA tend to be younger and demonstrate faster progression to the final stages of OA compared to those with OA of other lower extremity joints.[8] In the US alone, the annual direct health care expenses for lower extremity PTOA is approximately $3.06 billion.[50] Collectively, the high prevalence of ankle injuries and its relationship with the early onset of PTOA development may result in increased duration of pain and functional loss as well as an increased public health burden. Despite the known links between LAS, CAI, and PTOA and the evidence demonstrating the burden of LAS and its sequelae, early pathoetiological changes and how they can be assessed are poorly understood among researchers and practitioners. However, leveraging our knowledge about these changes and how they can be quantified will permit the assessment of how well therapeutic interventions can slow ankle PTOA progression.

Therefore, the purpose of this review is to review the plausible mechanistic links among LAS and its sequelae of CAI and PTOA as well as review techniques that can quantify talar cartilage health. Understanding the pathway from ligamentous ankle injury to ankle PTOA is vital to developing theoretically sound therapeutic interventions aimed at slowing ankle PTOA progression. However, assessing the effectiveness of such interventions must be based on direct markers of disease progression and cartilage health.

2. The pathway from ankle sprain to ankle PTOA

Despite the high incidence of ankle sprains and PTOA, the underlying etiology of ankle PTOA is not fully elucidated. It is theorized that joint degeneration after ankle sprains may result from damage to the articular surface at the time of ankle sprain (i.e. talar lesions) or from residual joint instability (i.e. altered loading).[10, 21, 49, 52]

2.1 Talar Condral Lesions

Previous data has observed that 89% of young patients (mean age of 19 years) with a severe acute ankle sprain had talar chondral lesions.[10] The talar chondral lesions are commonly found arthroscopically on the medial aspect of the talus in patients with acute LAS and CAI.[10, 52] During a typical LAS, it is speculated that the medial talar dome impacts the inner surface of the medial malleolus or tibial plafond, which may result in a talar osteochondral lesion on the medial talus. Empirical data also indicates that a partial or complete tear of the anterior talofibular ligament (ATFL) results in early degenerative changes in the anteromedial and anterolateral regions of the talar dome compared to an uninjured ankle[53] supporting this premise.

2.2 Altered Loading

Recurrent ankle injuries are also a leading cause of ankle PTOA.[49] Data suggests that 95% of CAI patients (mean age of 20 years) had chondral lesions that were graded as more severe than those in the acute injury group.[10] Although the exact mechanisms of how recurrent ankle sprains contribute to the development of ankle PTOA is unknown, altered joint contact stress is a theorized mechanism.[21] For example, Bischof et al[21] found that talar peak contact strain translated anteriorly and medially with increasing weight acceptance in the involved ankle of those with unilateral CAI. This altered joint contact strain, particularly over the long-term alterations, are likely the result of the residual sensorimotor[12], structural[13, 14], and/or biomechanical[15-19] changes observed in those with CAI. Indeed, each of these adaptation categories is considered a potential causal factor for early degenerative changes of the talar articular cartilage.[9, 20-22, 54] (Figure 2.1) The following section summarizes the evidence documenting the presence of these factors in those with LAS, CAI, and ankle OA, demonstrating the potential role that each domain could have in the development of ankle PTOA. Understanding their role will help develop therapeutic interventions that could intervene on ankle PTOA development.

2.2.1. Structural factors influencing ankle joint loading

Those with LAS, CAI, and PTOA show altered laxity at the ankle joint. Ankle sprains cause a disruption of the lateral ankle ligaments and as a result, disrupt passive restraint of the joint.[55] Previous research has shown residual joint laxity in those with acute LAS[56] and CAI[13] which may subsequently change ankle kinematics, shift cartilage contact strains, and eventually result in cartilage degeneration.[22, 54] For example, Bae et al[22] found that ankles with ruptured lateral ankle ligaments had increased and anteromedially translated joint contact pressures on the talus as participants progressed through the stance phases of gait. Similarly, Caputo et al.[54] showed that patients with chronic ATFL insufficiency had increased anterior and superior translations and internal rotation of the talus compared to intact ankles. This evidence suggests that joint laxity contributes to the initiation and progression of ankle PTOA. However, as ankle OA progresses to a more severe stage, the ankle joint typically become progressively stiffer,[57] likely due to the development of osteophyte growth. Ankle PTOA patients have demonstrated decreased laxity outcomes, possibly due to increased ankle joint stiffness.[58] Similarly, osteophytes and subchondral sclerosis were more prevalent in volleyball players with a history of ankle sprains compared to healthy controls.[59] Thus we speculate that osteophyte formation, due to altered contact stresses, ultimately result in joint stiffening. Future research is needed to prospectively quantify long-term prospective changes in ankle joint laxity and joint stiffness as an ankle sprain degenerates to confirm this hypothesis.

Dorsiflexion restrictions have been observed in those with LAS, CAI, and ligamentous ankle PTOA.[58, 60, 61] Sagittally, Denegar et al[56] reported restrictions in posterior talar glide in subjects with a history of a lateral ankle sprain. Similarly, Wikstrom and Hubbard[62] found that individuals with unilateral CAI had a significantly more anteriorly positioned talus in the involved limb relative to the uninvolved limb and the matched control group. During weight-bearing activities, these malalignments could contribute to alter ankle joint loading by restricting dorsiflexion range of motion. Reduced dorsiflexion has been reported in individuals with LAS and CAI[60, 61] in a variety of weight-bearing activities such as walking[63], jogging[64], and jump landing.[15] Limited dorsiflexion will limit an individual's ability to absorb impact forces with the gastrocnemius-soleus complex and result in increased stress being transmitted to the talar articular surface. In the frontal plane, individuals with LAS and CAI were more likely to be correlated with hindfoot varus malalignemnt.[8, 52]

Horisberger et al[65] reported that a varus alignment was the most prevalent (60.9%) in their patients with ankle PTOA. Under weight-bearing, this varus deformity leads to asymmetric loading distributions across the joint and increase contact stress on the medial aspect of the talus.[66] Noguchi[67] reported similar findings, illustrating that an ankle without lateral ankle ligaments had an increased stress distribution on the medial side of the ankle joint. Although there are similar patterns in structural changes among LAS, CAI, and ankle PTOA, prospective studies are needed to investigate the long-term effects of altered joint laxity, range of motion, and joint alignments following ankle sprains on cartilage health.

2.2.2. Sensorimotor factors influencing ankle joint loading

Sensorimotor deficits following a LAS are broad in nature as impairments have been noted in alpha motor neuron pool excitability, strengths, and postural control.[12] Reduced strength at the ankle joint is commonly observed across LAS[60, 68-70], CAI[14, 71-73], and ankle PTOA[58] individuals. This is consistent with other findings suggesting that ankle OA patients have less isometric dorsiflexion and plantar flexion torque production compared to the contralateral ankle and a control group.[74, 75] An explanation of this reduced strength and torque production in CAI and ankle OA patients might be muscle atrophy. Evidence for muscle atrophy has been found in both CAI[76] and ankle OA patients.[74, 75, 77] For example, the intrinsic foot muscles and soleus muscle volume measured by MR Imaging in individuals with CAI was smaller than healthy controls.[76] Similarly, quantitative MR imaging analysis showed a significant cross-sectional area reduction in soleus muscle in the involved limb of ankle PTOA patients compared to the healthy limb,[77] and decreased circumference in lower leg.[74, 75, 77] Another possible mechanism of the decreased strength is arthrogenic muscle inhibition (AMI). AMI is an ongoing reflex inhibition of the musculature surrounding an injured joint, and is measured by assessing motoneuron pool excitability (MNPE).[78] Altered MNPE indicates changes in the number of available motor neurons responding to an excitatory stimulus.[78] A study indicated facilitation of the soleus MNPE and an inhibition of the tibialis anterior MNPE in an involved LAS limb compared to the healthy limb.[79] Previous research also found decreased alpha-MNPE of the soleus[80] and peroneus longus[80, 81] in CAI patients. While no study has investigated the MNPE in those with ankle PTOA, patients with knee OA had reduced quadriceps MNPE, which diminish voluntary quadriceps activation and this was hypothesized to contribute to the quadriceps weakness identified in the study sample. Therefore, AMI and/or muscle atrophy in those with CAI could contribute to muscle weakness, as OA progresses and/or contribute to PTOA. Either mechanism could negatively influence joint stability by decreasing shock absorption during dynamic activities. However, longitudinal studies are needed to understand how strength deficits post ankle sprain and their underlying mechanisms influence the development of ankle PTOA.

Postural control deficits are consistently found in individuals after an acute LAS and in those with CAI.[82-85] Indeed, ankle PTOA patients who had a history of ankle sprains also showed static balance impairments compared with the healthy group.[58] It is theorized that altered postural control results from the damaged mechanoreceptors at the time of the index sprain.[86] Supporting this hypothesis, individuals with CAI showed decreased sensitivity of the plantar cutaneous mechanoreceptors,[87, 88] which has been linked to worse balance.[87] A recent study found that worse static postural control was associated with lower proteoglycan density within the talar articular cartilage in individuals with CAI.[25] Dynamic postural control deficits has been also shown in those with CAI.[19, 89-91] Specifically, individuals with CAI demonstrated longer time to stabilization and unstable postural control during a single leg landing task.[19, 89-91] Interestingly, this longer time to stabilization after a single leg jump landing correlated with worse cartilage composition in those with CAI.[23] While the current evidence indicates that CAI associated postural control impairments correlate to markers of early degenerative changes, the exact mechanisms are still unknown. Altered postural control may be the result of compensatory strategies that the foot and ankle complex uses to accommodate for the proprioceptive and neuromuscular insufficiencies caused by the injury. Thus, the constraints of the sensorimotor system (i.e. poor postural control) may lead to alterations in the lower extremity joint kinematics and kinetics in order to complete the task, which leads to altered joint loading. However, further research is needed to understand the relationships among postural stability, joint biomechanics, and joint loading.

2.2.3. Biomechanical factors influencing ankle joint loading

Altered biomechanics during the loading response phase of various activities would change joint contact stress patterns and potentially lead to early talar cartilage degeneration. The most common alterations among those with LAS and CAI in the stance phase of gait cycle is increased inversion at initial contact in the injured limb compared to uninjured individuals.[16, 17, 92] Similarly, CAI patients had a more inverted ankle and foot position while running compared to the healthy controls.[63, 93] This inverted position may create an external load that further forces the ankle into inversion, resulting in giving way episodes and recurrent ankle injuries. This position likely increases stress on the medial portion of the tibiotalar joint similar to a varus malalignment. In vivo evidence would support this hypothesis as increased cartilage contact strains are noted in anteromedial aspect of the talus during the stance phase of walking in those with CAI.[21, 22] Individuals with CAI also showed increased vertical ground reaction force and loading rate during walking[94, 95] and running[96] compared to healthy individuals, which could increase the stress on the ankle joint. Cumulatively, the data suggest that altered kinematics alter the loading/strain patterns on the talar cartilage, which could contribute to the development of ankle PTOA. However, some evidence showed that individuals with PTOA demonstrated decreases in ground reaction force and loading rate during walking relative to age-matched controls. [97, 98] It may be speculated that these alterations are designed to protect against pain and may be in part due to several factors including a stiffer joint and muscle weakness. For example, ankle OA associated muscle atrophy and weakness in conjunction with increased soft tissue stiffness results in restricted ankle movements[98-100] as well as reduced ankle joint moments and powers during walking that ultimately reduced ankle joint loading.[74, 98, 99] These altered biomechanical profile in ankle PTOA patients manifest as slower walking speed, shorter step length, shorter single support time during walking.[98, 101]

Individuals with CAI have also been shown to have different kinematic and kinetic patterns during jump landings compared with controls. Those with CAI exhibited decreased total angular displacement of ankle joint and decreased time-to-peak vertical ground reaction force concomitant with less eccentric sagittal plane power generation during a single-leg jump landing compared to healthy individuals.[15] Similarly, CAI patients displayed less plantar angles which coincided with a lower plantarflexion moment relative to copers and controls during the sing-leg landing phase from maximal vertical forward jump.[102] This evidence indicates that CAI patients had less ability to attenuate impact force, which may lead to increased stress being transmitted to the ankle joint structures (i.e. cartilage, ligaments). There is limited evidence about movement pattern alterations during walking, running, and jump landings in those with LAS and ankle OA. It might be due to pain and/or the difficulty to complete the tasks in these populations. However, we speculate that altered kinematic and kinetic patterns would be present and that the long-term presence of kinetic and kinetic alterations play a role in the development of ankle PTOA. Therefore, longitudinal research is needed to determine the how aberrant movement patterns in those with ankle sprains or instability affect cartilage health and the development of ankle PTOA.

2.3. Summary of factors influence ankle joint loading

Ligamentous ankle PTOA is thought to have a multifactorial etiology, much like the causal mechanism of CAI is thought to be multi-factorial. Throughout this review, similar structural, sensorimotor, and biomechanical impairments were observed along the pathway from an acute lateral ankle sprain to ankle PTOA. (Figure 2.2) Cumulatively, the literature would suggest that the initial impairments induced following an acute lateral ankle sprain initiates a cascade of events that not only leads to the development of CAI but also initiates the degeneration of the talar cartilage. Based on this evidence, prospective research is needed to determine the exact contributions and timing of those events to learn more about they interact to generate the hypothesized mutli-factorial mechanism responsible for the development of ankle PTOA. However, the current literature is limited solely to surrogate measures of talar cartilage health (e.g. biomechanics and contact stress) which do not provide the information necessary to determine if interventions are having a positive impact at slowing PTOA progression.

3. Quantifying ankle cartilage health

The mean thickness of talar cartilage is 0.94-1.62mm, which is about half of that of femoral cartilage.[103] The smaller size compared to the knee, results in translating higher force per area to the ankle joint while loading.[104, 105] However, the extracellular matrix of ankle cartilage is more dense than that of knee cartilage. The properties of the ankle cartilage (higher dynamic stiffness and compressive modulus) increase resistance to compressive loads,[106] which may explain the lower prevalence of ankle OA compared to knee OA.[107]

Due to its size and properties, quantifying talar cartilage health is challenging. Most findings of cartilage health decline have been from visualizating the structure during surgical procedures.[108] [10, 109, 110] [111] For example, one study noted that 21% of CAI patients had degenerative changes at the ankle joint at the time of surgical reconstruction procedures[108] while others noted that between 40% to 95% of those with CAI were found to have degenerative changes or osteochondral lesions via arthroscopic procedures.[10, 109-111] While ankle arthroscopy is considered a superior method for determining intra-articular abnormalities because it allows direct visualization of the site, it is not appropriate for broad clinical application. Thus, noninvasive diagnostic modalities were developed to detect intra-articular lesions.

Conventional/traditional magnetic resonance (MR) imaging technology allows in vivo high resolution visualization of the cartilage and is thought to be a more sensitive tool for detecting osteochondral lesions at the ankle joint compared to radiographic evaluation.[112-114] Using MR imaging, previous research[115] found that 41.5% of patients with an ankle sprain between 6-12 prior to study undergoing the scan, regardless of the presence of persistent complaints, had a K&L grade of at least 1. Further, this early sign of OA was observed more frequently in injured ankles compared to uninjured ankles.[116] MR imaging is also 95% sensitive to the grade for osteochondral lesions of the talus when compared to arthroscopic evaluation.[113] Cha et al. reported MR Imaging showed a sensitivity of 75% and 100% for grade 3 and grade 4 of cartilage lesions respectively in those with CAI. However, there is poor sensitivity for grade 1 (10%) and 2 (42%) osteochondral lesions of the talus.[111] This study may indicate that the conventional MR protocol may struggle to detect early degenerative changes of the ankle cartilage in LAS and CAI patients. Detecting subtle changes in the early stages of OA is important because there is no effective treatments for OA once this joint disease has become severe.

Currently, more advanced MR imaging techniques allows us to quantify the biochemical changes in the articular cartilage by assessing the quantities of the primary structural elements of the cartilage: water and the extracellular matrix (ECM). The ECM is composed of type II collagen, proteoglycans, and glycosaminoglycans. [117, 118] Type II collagen fibrils in cartilage are organized into a structural framework that serves to stabilize the matrix and contributes to the shear and tensile properties of the tissue.[117, 118] Proteoglycans interact with the water and create the swelling pressure that provides compressive stiffness.[117, 118] Therefore, proper composition and distribution of the biochemical components is essential for normal cartilage function. In the earliest stages of OA development, proteoglycans are initially depleted resulting in the collagen matrix beginning to break down. This breakdown occurs without morphological changes but leads to greater permeability to water.[119]

A quantitative T2-mapping technique allows for the assessment of water and collagen content as well as the collagen orientation in cartilage.[117] Changes In the structural integrity of the collagen matrix and water content are associated with increased T2 relaxation time. Using this method, Lee et al.[53] found that an anterior talofibular ligament (ATFL)-deficient ankle group showed a higher talar cartilage T2 value compared to an uninjured group even though the injured group was younger. Similarly, other studies[28, 120] found that young CAI individuals had higher T2-relaxation times in the talar cartilage relative to healthy individuals, supporting the association between ankle instability and early onset of PTOA.

While T2 values are insensitive to changes in proteoglycan concentration,[117] T1rho mapping methods are. Previous studies report that higher T1rho relaxation times are associated with lower proteoglycan density in cartilage.[121, 122] Utilizing the T1rho MRI, research has shown lower proteoglycan density in the femoral and tibial articular cartilage as early as 1-year following ACL reconstruction.[123-125] However, there is a scarcity of T1rho relaxation time data for ankle cartilage. To date, only a single investigation has used T1rho and reported that CAI patients had a higher T1rho relaxation times in the talar cartilage compared to uninjured healthy individuals.[29] Cumulatively, this data suggests decreased proteoglycan density and increased water content in the talar cartilage of those with CAI, which may be the indicative of early OA onset.[123, 124, 126]

While compositional MR techniques have been shown to be sensitive measures of cartilage health,[127] MR imaging is expensive and not easily available for serial evaluation of cartilage health clinically. Ultrasonography (US) is an alternative measurement tool for quantitatively assessing cartilage thickness in a clinical setting. The decline of cartilage thickness is one of the hallmark characteristics of OA.[128] US measures of cartilage thickness in the knee joint were moderately to strongly associated with thickness measures of T1 weighted MR imaging, suggesting that US can be used to assess knee joint cartilage health.[35, 127] Similarly, our preliminary data also showed that US thickness was correlated to the MR volume. Thus, US may be a cost-effective and more accessible tool to evaluate talar cartilage morphology but future research is needed to test this hypothesis.

Although cartilage thickness (i.e morphology) provides an estimate of overall joint health, it may not be the most sensitive marker for early stage OA because compositional changes occur prior to declines in cartilage thickness.[119] Therefore, more robust clinically based methods should be explored. For example, quantifying how the cartilage responds to and recovers from loading could represent more robust measures because composition determines the behavior of cartilage.[32] Using MR imaging, there is in vivo evidence that cartilage deformation and recovery under physiological loading conditions in healthy individuals is quantifiable. For example, 60 single leg hops resulted in decreases in talar cartilage thickness corresponding to strains of 2%.[129] Van Ginckel et al[33] showed that the mean volume of talar cartilage decreases by 14.6% after 2 minutes of single leg standing and by 12.5% after 10 single leg drop jumps from a 40cm box. These authors also showed that talar cartilage deformed about 10% following 30 squat exercises and restored to normal volume within 30 minutes.[34] With the same exercise protocol (30 squat exercises), T2 mapping revealed increases in T2 relaxation times (+16.1%) within the talar cartilage.[130] Previous studies found US imaging is sensitive enough to quantify cartilage deformation and recovery rates at the knee joint following various loading activities.[131, 132] However, no studies have quantified ankle cartilage deformation and recovery following weight bearing activities using US at the ankle. A measure of cartilage deformation and recovery could provide an indicator of cartilage resiliency, which may indicate overall cartilage health in those suspected to be in the early stages of ankle OA development better than morphologic measures alone.[31, 133]

Although general cartilage metabolism (i.e. mediators, biomarkers) in OA are well known,[134] *in vivo* regulation of biochemical consequences of ankle PTOA is still relatively unknown. Schmal et al.[135] identified that agreecan (an integral part of the extracellular matrix) and BMP-7, taken from synovial fluid, were positively associated with duration of symptoms, self-reported foot and ankle functions, and radiographic Kellgren Lawrence score (KLS) of the ankle in those with early stage ankle PTOA (mean age of 32.6±13.6). Schmal et al.[136] also found that IGF-1 /IGF-1R (marker of intrinsic cartilage repair) levels were negatively associated with osteochondritis dissecans (OCD) grading, degree of cartilage damage, self-reported foot function, and KLS in individuals with OCD (mean age of 30.7 ± 14.8). Adams et al[137] identified elevated inflammatory cytokines (IL-1Ra, IL-6, IL-8, IL-10, IL-15, and MCP-1) in the synovial fluid of end-stage ankle PTOA compared to healthy controls. These data offer possible diagnostics and interventional strategies. However, the regulation of biomarkers could differ depending on progress of ankle degeneration and sampling technique (e.g. synovial vs blood biomarkers). Therefore, further research is needed to better understand of OA biochemistry at the ankle joint and establish reliable biomarkers that are sensitive and specific to the earliest changes in ankle joint with ligamentous injury.

4. Conclusion

LASs are the most common musculoskeletal injury sustained during daily life and sport. The causal mechanism of CAI, and ligamentous ankle PTOA, sequela of LAS, appears to be multi-factorial based on the consistent presence of structural, sensorimotor, and biomechanical impairments (e.g. reduced ROM and strength, and postural control deficits, and altered biomechanics) across the conditions. Each of these adaption domains contribute to altered ankle joint loading and subsequently the breakdown of talar cartilage. The presence of consistent impairments provides evidence that rehabilitation strategies that could slow ankle PTOA progression should be comprehensive in nature and address range of motion, strength, balance, and movement patterns. However, these intervention recommendations are based on direct measures of cartilage health. Assessment of intervention strategies should be based on direct measures of talar joint health (e.g. imaging) in order to directly determine if current and novel intervention strategies are able to slow the progression of ankle PTOA.

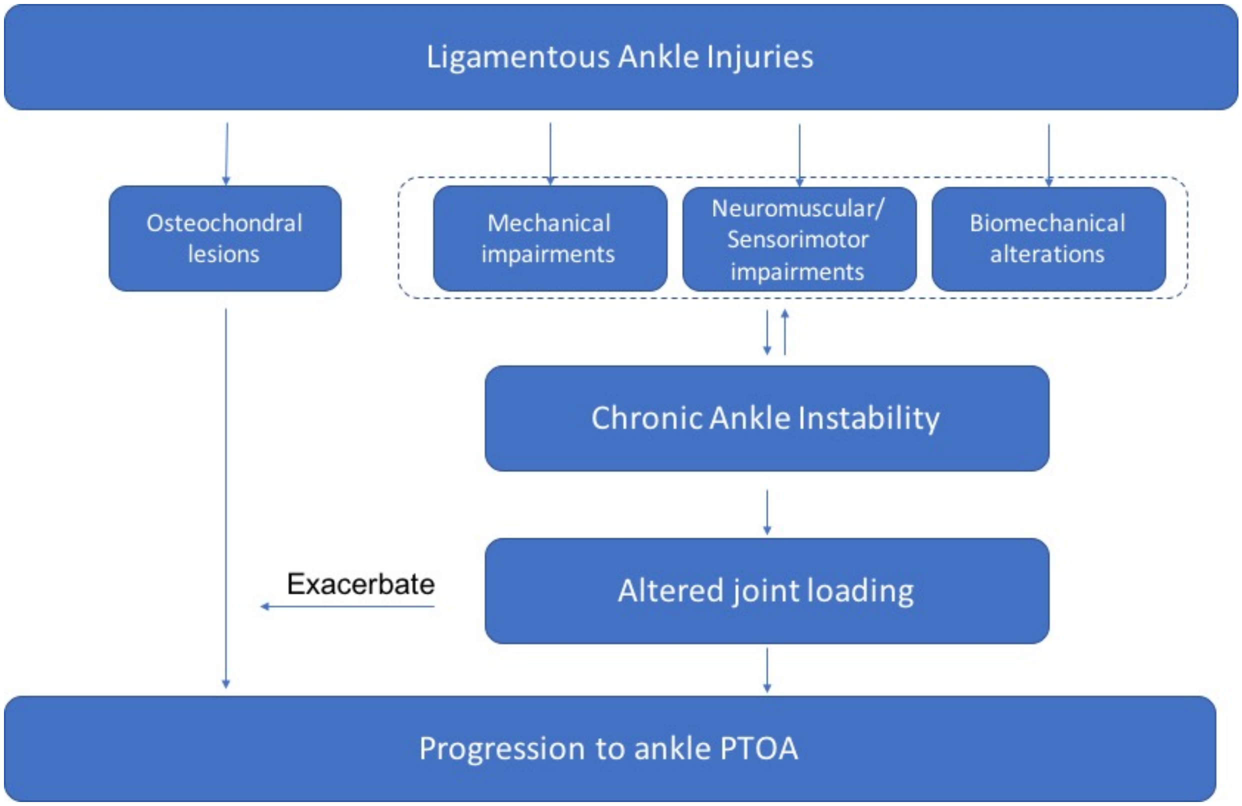


Figure 2.1. The plausible pathway from ankle sprain to ankle post-traumatic osteoarthritis.

	Acute LAS	CAI	Ankle OA
Mechanical factors	• ↑ Joint laxity • ↓ ROM	• ↑ Joint laxity • ↓ ROM • Structural malalignments	• ↓ Joint laxity • ↓ ROM • Structural malalignments
Neuromuscular/ sensorimotor factors	• ↓ Strength • ↓ Postural control	• ↓ Strength • Muscle atrophy • ↓ motoneuron pool excitability • ↓ Postural control	• ↓ Strength • Muscle atrophy • ↓ Postural control
Biomechanical factors	• ↑ inversion during walking • ↑ and shifted anteromedially joint contact stress	• ↑ inversion during walking • ↑ and shifted anteromedially joint contact stress • ↓ ankle angular displacement and ↓ time-to-peak vGRF during landing	• ↓ ankle movement during walking

Figure 2.2. Summary of factors influencing ankle joint loading in those with lateral ankle sprain, chronic ankle instability, and ankle osteoarthritis.

CHAPTER 3: METHODS

EXPERIMENTAL DESIGN

To achieve Aim 1, this study will utilize a mixed-model design. The between factor will be Group (CAI, Control) while condition (Non-loading, static loading, dynamic loading) and Time (Pre, Post) will be within factors to assess differences in cartilage deformation. To achieve Aim 2 & 3, a correlational design will be used. Each participant will complete three test sessions (1: patient-, cilnian-, laboratory-oriented outcomes, 2: standing loading condition, 2: Hopping loading condition) that will be separated by at least 1 day between session 1 & 2 and 1 week between session 2 & 3. The order of loading conditions will be counterbalanced within each group. The primary dependent variables will be change (i.e. deformation) in raw cartilage thickness and cross-sectional area which will be expressed as a percent difference from the baseline values. A diagram outlining the overall study design is shown in Figure 3.1.

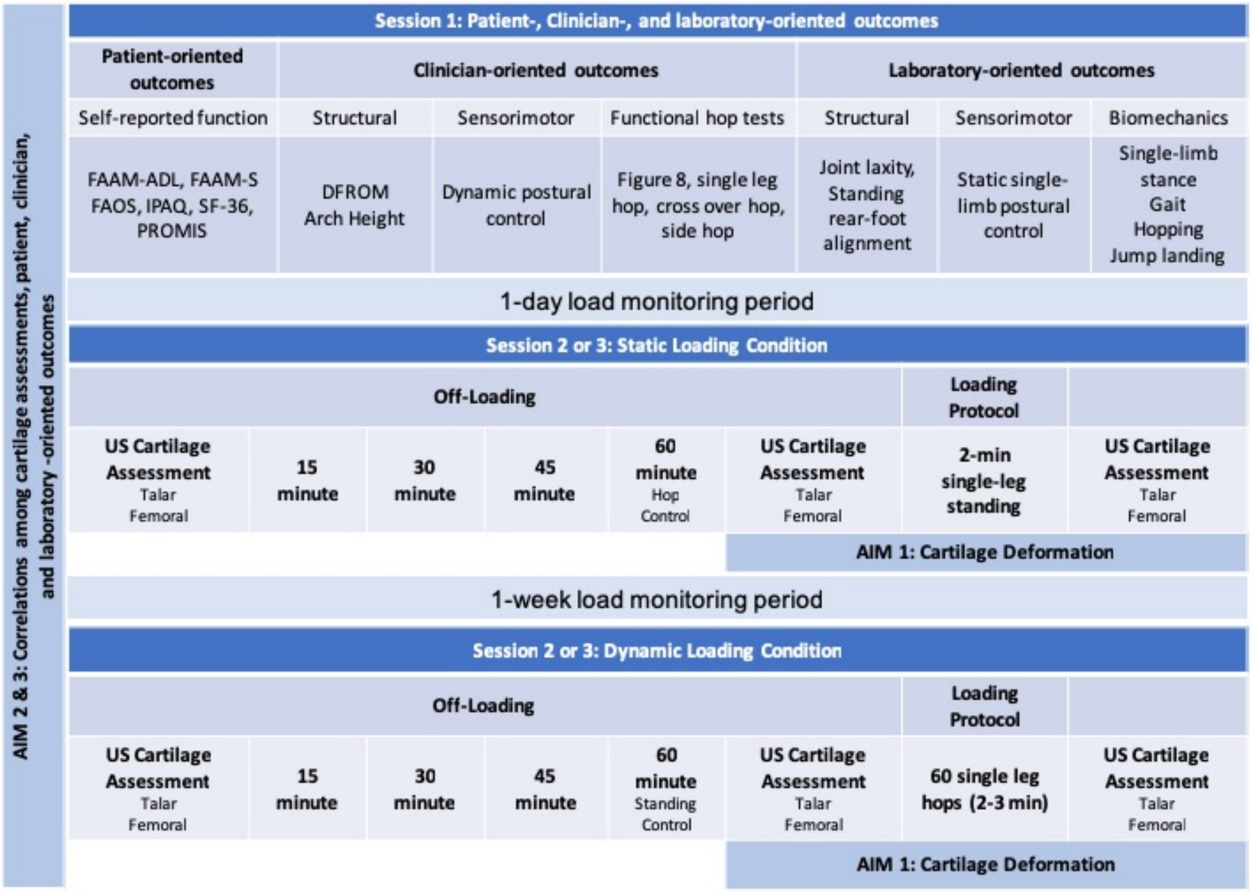


Figure 3.1. Overall study design diagram.

METHODS

Participants

We plan to recruit and enroll a total of 60 participants (30 with CAI and 30 healthy individuals). Participants in both groups will be required to be between 18 and 35 years in age. The inclusion criteria for healthy individuals include being free from: (1) a history of ankle sprains; (2) acute lower extremity and head injuries for the previous 3 months; (3) known equilibrium disorders; and (4) chronic lower extremity pathologies. Healthy individuals will score <11 on the Identification of functional ankle instability (IdFAI) (Appendix 1). CAI will be defined as those individuals who: (1) have sustained at least two lateral ankle sprains; (2) have experienced at least one episode of giving way within the past 6-months; (3) score of >11 on the IdFAI. These criteria are in agreement with the guidelines established by the International Ankle Consortium's recent position statement.[138] Exclusion criteria for the CAI group will include known vestibular and vision problems, acute lower extremity and head injuries (<3 months), chronic musculoskeletal conditions (e.g., symptoms of OA, ACL deficiency) and a history of ankle surgery to fix internal derangements.[138] Self-reported function, as measured by the Foot and Ankle Ability Measure (FAAM) will be assessed but not used as an inclusion criterion consistent with the recommendations of the International Ankle Consortium.[138] Those with bilateral CAI are allowed to participant and the limb with worse IdFAI scores will be considered the involved limb.

Power analysis

An *a prior* power analysis was completed using G*power (Vesion 3.1.9.3) to determine the sample size needed to detect significant differences between groups and correlations among outcomes in CAI group. Since no previous investigation has directly captured the outcomes of interest in those with CAI, we conducted the pilot test with 4 CAI individuals and 3 healthy controls. For aim 1, we calculated the effect sizes (d=0.05 to 0.59) of group differences on medial and lateral talar cartilage deformation after standing and hopping loading protocols. For aim 2 & 3, there are significant correlations (r=0.739-996) among talar cartilage deformations, patient-, clinician-, and laboratory-oriented outcomes. Based on the pilot testing results with an $\alpha = 0.05$, and power ($1-\beta$) of 0.8, a sample size of 30 participant in each group will allow us to determine statistical difference in talar cartilage deformations between groups and correlations among outcomes in CAI individuals.

Procedures

Once eligible, participants will report for the first test session. They will read and sign the consent form. Then, the patient-, clinician-, and laboratory-oriented measures will be assessed for the involved limb of the CAI group and the dominant limb of the control group. After the first session, participants will be outfitted with a wearable tri-axial accelerometer (Secondary Research Question), the ActiGraphGT9X Link (ActiGraph Corporation, Pensacola, FL). The GT9X has the capacity to capture and store high-resolution human activity information, and it has been shown to be valid and reliable for reporting steps-per-day and minutes of moderate-to-vigorous physical activity in young, active cohorts.[139, 140] The next day, participants will be asked to wear the accelerometer per manufacturer guidelines for at least 24 hours until the start of their second test session. In this session, participants will complete either the static or dynamic loading protocol based on the counterbalanced order of testing sessions. Following the second test session, participants will be asked to wear the accelerometer for another 7-day period until the start of the third test session. In the third session, participants will complete the remaining loading protocol.

Participants will be instructed that they can remove the accelerometer for bathing and sleeping, but that it should be worn at all other times throughout the day. Participants will also self-report times that they exercised during the activity monitoring using an exercise log. Average steps-per-day and average moderate-to-vigorous physical activity/day will be extracted from ActiLife software for the 24-hour and 7-day periods and normalized to the number of wear days for each participant. Cumulative loading will be estimated based on laboratory vertical ground reaction force and steps-per-day$_{MVPA}$.

Ultrasonography

Off-loading period

Prior to the completion of each loading condition, all participants will complete an off-loading period of 45 minutes to minimize the effect of preceding activity on the cartilage.[132] During this period, all participants will sit on a padded plinth with their back against a wall while in a long-sit position and ultrasonographic images of talar and femoral cartilage will be captured every 15 minutes. Then, participants will complete a control condition that will consist of an additional 15 minutes of off-loading before completing one of the loading conditions.

Loading protocols

For the static loading condition, participants will stand on an involved limb with 20 degrees of knee flexion for 2 minutes.[33] During the standing, they will be allowed to have their fingers on a wall to assist with balance. For the dynamic loading condition, participants will complete a series of 60 single leg forward hops.[129] Each hop will be 24 inches in distance. During the hopping protocol, an accelerometer will be on the shank to monitor the magnitude of loading. Participants will be given an opportunity to practice the hopping procedure should they wish. Participants will also be told to place their non-hop leg down to regain their balance should they need to. Talar and femoral cartilage will be scanned immediately followed by each loading protocol.

Ultrasonographic image

Ultrasonographic images of the talar and femoral (Secondary Research Question) cartilage will be acquired using the Phillips Lumify tablet-based ultrasound unit (Amsterdam, Netherlands) with a 12-MHz linear probe. This system was chosen for its increased portability and reduced cost, relative to traditional ultrasonography units. For talar cartilage, participants will be positioned with their back against a wall and their knee positioned to 90 degrees of flexion and their ankles at foot flat position (~50 degrees of plantar flexion) (see Figure 3.2.A).[141] The probe will be placed transversely in line with the medial and lateral malleolus and rotated to maximize reflection of the articular cartilage surface. For femoral cartilage, participants will be positioned with their back against a wall and their knee positioned to 140 degrees of flexion using a manual goniometer (see Figure 3.2.B).[131] The probe will be placed transversely in line with the medial and lateral femoral condyles above the superior edge of the patella and rotated to maximize reflection of the articular cartilage surface.[131, 142, 143] A tape measure will be secured to the treatment table, and the distance between the wall and the posterior calcaneus will be recorded for ankle and knee measures to ensure consistent participant positioning across all time points.[131] A transparency grid, placed over the US screen ensures probe placement consistency across time. Three images at each time point will be capture and averaged for further analysis. After each session, the US images will be blinded and the file names will be changed in a random order.

Talar and femoral cartilage images will be manually segmented using ImageJ software (National Institutes of Health, Bethesda, MD, USA). The cartilage will be segmented to identify the medial and lateral cross-sectional area (mm^2). This will be done by visualizing the entire cartilage volume on the medial and lateral sides of the respective joints (see Figure 3.2.C and 3.2.D).[132] Area will be normalized to the length of the cartilage-bone interface to get average thickness (mm). Our preliminary data has demonstrated excellent intra-rater reliability with this technique (ICC=0.93-0.97). In addition to the raw thickness and cross-sectional area scores, percentage change scores will be calculated for deformation at all time points using the following formula. Percentage $\Delta = [(mean_{post} - mean_{pre}) / (mean_{pre})] *100$.[132] A greater negative percentage change in thickness and cross-sectional area indicates greater cartilage deformation.

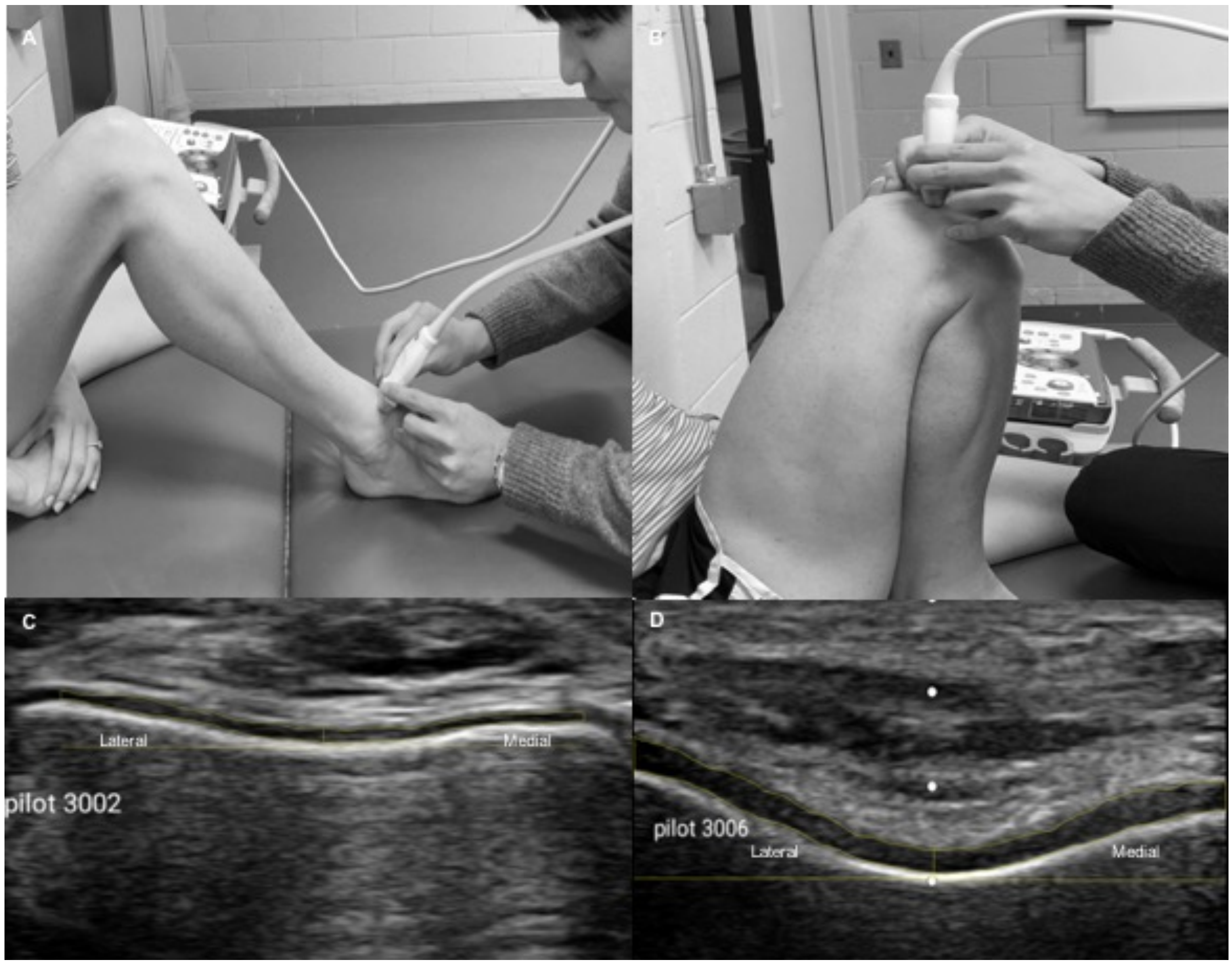


Figure 3.2. Ultrasonography set up and participants positioning for A) talar and B) femoral cartilage. Ultrasonography outcome measures for C) talar and D) femoral cartilage.

Patient-Reported Outcomes

While waiting for the ultrasound images of the talar and femoral articular cartilage to be taken, participants will complete several questionnaires of self-reported function. Patient reported-outcomes will include the Foot and Ankle Ability Measure (FAAM) and the FAAM-

Sport (FAAM-S), the International Physical Activity Questionnaire (IPAQ) short form, the Foot and Ankle Osteoarthritis Scale (FAOS), and short form-36 (SF-36). The FAAM (Appendix 2) assess physical function related to daily living (21 items) and sport (8 items) with scores ranging from 0 to 100%.[144] Both FAAM and FAAM-S scores have been found to be reliable and precise (*r=0.89*, SEM= 2.1 and *r=0.87*, SEM= 4.5, respectively) in people with CAI.[145] The IPAQ (Appendix 3) has 7 items to determine the kinds of physical activity and the intensity and volume of physical activities.[146] The IPAQ has been shown to be a reliable (r=0.80) questionnaire for monitoring population levels of physical activity[147] and has been shown to detect difference between those with CAI and healthy controls[148]. The FAOS (Appendix 4) is a 42-item questionnaire assessing patient-relevant outcomes in 5 subscales (pain, other symptoms, activities of daily living, sport and recreation function, foot and ankle-related quality of life).[149] The FAOS has been shown to possess good reliability (ICC=0.70-0.92) and moderate validity (r=0.58-0.67) in lateral ankle instability patients.[149] The SF-36 (Appendix 5) comprises 11 main questions subdivided into 36 items, with higher scores representing a better state of health. The SF-36 has been tested for reliability and validity[150] and has been shown to detect difference between CAI and healthy control groups.[151] Lastly, the Patient-Reported Outcome Measurement Information System (PROMIS) measures of global health, physical function, and ability to participate in social roles and activities will be included. PROMIS has been shown to possess good reliability and validity in general population and individuals with chronic conditions.[152-154]

Structural Alignment

Ankle joint laxity and dorsiflexion range of motion will be assessed. An instrumented ankle arthrometer (Blue Bay Resarch Inc, Navarre, FL) will quantify the anterioposteror (AP) load-displacement and inversion-eversion rotational laxity characteristics of the involved and matched control ankle joint complex.[155] The test-retest reliability of quantifying ligament laxity with this type of arthrometer is good to excellent (0.82-0.97).[156] For AP displacement, the ankle will be loaded with 125N of anterior and posterior force after starting in a neutral position. For rotational laxity, the ankle will be loaded to 4Nm of torque in each direction. Three trials in each direction will be taken and averaged for further analysis.

Dorsiflexion range of motion will be assessed using the weight-bearing lunge test (WBLT).[157] This test requires participants to perform a modified lunge to determine the farthest distance the great toe can be from a wall (cm), when the ipsilateral knee can touch the wall without the heel lifting from the ground. The WBLT is a reliable measure of dorsiflexion range of motion (ICC=0.80-0.99).[158]

Static arch height will be assessed using the navicular drop test.[159, 160] The displacement of navicular tuberosity height between in the subtalar neutral position while participant is seated and in a weightbearing position while the participant is standing. The subtalar neutral position will be defined as equal palpation of the medial and lateral aspects of the head of talus. This method has shown to moderate to good reliability (ICC=0.73-0.96).[160]

Standing rearfoot alignment will be measured using a digital photograph taken while the participant is placed in the weight-bearing position (standing) and in non-weight-bearing position (prone).[161, 162] The rearfoot angle will be measured between the lower leg line (the centerlic line of the posterior aspect of the lower leg and Achilles tendon) and calcaneus line (the centerlince line of the calcaneal tuberosity) using ImageJ software (National Institutes of Health, Bethesda, MD, USA). The ICC for intrarater reliability and interrater reliability of this assessment were 0.91 and 0.93, recpectively.[161]

Biomechanics

Walking gait,[17, 163-166] hopping,[167, 168] jump landing,[23, 89, 169] and stance[170] biomechanics will be assessed. Three-dimensional kinematics (sampled at 120Hz, low pass filtered at 10Hz) and kinetics (1200Hz, low pass filtered at 75Hz) will be obtained during all tasks using a 10-camera Vicon motion capture system. Participants will be outfitted with 29 retro-reflective markers bilaterally on the following bony landmarks: acromion process, manubrium, anterior superior iliac spine, a rigid cluster of three markers on the sacrum, L4-L5 vertebral space, greater trochanter, anterior thigh, medial and lateral femoral condyle, anterior shank, medial and lateral malleoli, calcanei, and the first and fifth metatarsal heads.[164] Then, a static trial will be captured with the participant standing with arms across the chest to estimate the location of the landmarks needed to calculate joint centers.[164] After the static trial, the markers on the medial malleoli and femoral condyle will be removed.

During gait trials, participants will walk at a self-selected speed over multiple embedded force plates. Speed will be enforced with timing gates centered over the force plates during the five practice trials though a six-meter walkway. Then, five walking test trials will be collected. The trial will be accepted for data analysis if 1) both feet hit a single force plate individually, 2) gait speed is within a range (between above and below 5% of the average speed that is determined during five practice trials), and 3) participant maintain to look forward and gait kinematic are not altered during the trials.[164] For stance biomechanics, three, 20-s single limb stance trials will be completed.[170] The participant will stand on the involve limb with hands on their hips for all trials. Trials will be discarded if the non-stance limb touches down or if there is significant uncontrolled trunk movement during the trial.

Participants also will complete five trials of hopping biomechanics at a distance of 61 cm (24 inches) away from the center of the force platform.[129] This trial is consistent with the actual hops to be completed during the loading protocol. The participant will start each trial by standing on the involved limb and hop to the force plate. A successful trial will require the participant to land on the force plate and balance for 2 seconds.[129, 167, 168] Jump landing biomechanics will be assessed with landing error scoring system protocol that requires participants to jump from a 30cm platform placed at a distance of 50% of the participant's height away from the edge of the force platform, with an immediate rebound jump for maximum height.[171] Five successful trials will be collected. In order to be a successful trial, 1) required to jump the box with both feet at the same time, 2) land on the force plates, 3) jump straight up as high as possible immediately after landing, and then 4) land on two feet back on the force plates.[171]

Kinematics will include mean values of ankle joint angular ranges (maximum value-minimum value) for standing and ankle joint angle at initial contact that are identified as the point in the trial when the vertical ground reaction force (vGRF) >10N for walking, hopping, and jump landing tasks. Kinetic variables will include loading rates (the slop of the vGRF-time curve) and peak vGRF which will be normalized by participants' body weight.

<u>Sensorimotor Function</u>

Static and dynamic postural control will also be assessed. An AMTI force plate (AMTI; Watertown, MA) will be used to conduct the single limb static stance tests that will produce center of pressure (COP) outcomes in the anteroposterior (AP) and mediolateral (ML) directions. Three 10-s trials with eyes open and three 10-s trials with eyes closed will be collected, averaged, and used for further analysis. Force plate data will be collected at 50Hz and then filtered using a fourth order, zero lag, low pass Butterworth filter with a cutoff frequency of 5Hz.[172] This protocol generates reliable and precise data ($ICC_{2,1}$=0.34–0.87) in people with CAI.[172] The primary static postural control outcomes will include COP velocity and TTB mean in the AP and ML directions. Measures of static balance have been correlated to talar compositional health in those with CAI.[25]

Dynamic postural control will be assessed using a clinician-oriented outcome. Participants will complete three trials of three Star Excursion Balance Test (SEBT) in the anterior, posteriomedial, and posteriolateral direction as previously reported.[173] Reach distances will be normalized to the participant's leg length (i.e. anterior superior iliac spine to ipsilateral medial malleolus) before being used for further analysis. Normalized SEBT reach distances are a reliable measure of dynamic balance ($ICC_{2,1}$=0.85-0.96).[173]

Functional hop testing

Participants will perform four different unilateral hopping tasks that are commonly used to evaluate motor function in the clinical setting.[174] The hop tests include figure-8 hop, side-to-side hop, triple-crossover hop for distance, and single leg hop for distance tests (Appendix 6).[174] The figure-8 test (figure A, Appendix 6) requires the named pattern over a 5-meter distance outlined by cones. Participants will be instructed to hop as quickly as possible twice thorough the course on the involved limb. The side-to-side hop test (figure B, Appendix 6) requires 10 side to side single limb hops of 30cm distance as quickly as possible. Both figure-8 and side-to-side hop test will be recorded to the nearest 10th of a second. The triple-crossover test (figure C, Appendix 6) requires hop 3 times from a start line in a zigzag fashion, crossing over a line that will be 15cm wide. The single-leg hop test (figure D, Appendix 6) requires hop forward as far as possible. Both triple-crossover and single-leg hop tests will be recorded as the distance from the starting line to the heel position at the end of the jump. Each participant will be instructed on how to perform the tests and allowed practice trials for each test until they feel comfortable with the testing procedures. Three test trials will be recorded for each test and the best scores will be used for analysis. All participants will be allowed 30 seconds of rest between trials and a 1-minute rest between tests. If a participant does not perform the task correctly (i.e. unable to maintain balance upon landing, touched the contralateral limb to the floor), then that test trial will be discarded and repeated.

Statistical Analysis

Specific Aim 1: To determine if talar cartilage deformation using ultrasonography following a standardized standing and hopping protocols differs between those with CAI and healthy controls.

Research Questions

1.1. Cartilage thickness changes following the static loading protocol will be assessed using three (overall, medial, lateral) separate 2-way (Group (CAI and control) X Time (pre and post)) repeated measure analysis of variance (ANOVA) to determine if difference existed in cartilage deformation between the groups.

1.2. Cartilage thickness changes following the hopping loading protocol will be assessed using three (overall, medial, lateral) separate 2-way (Group (CAI and control) X Time (pre and post)) repeated measure analysis of variance (ANOVA) to determine if difference existed in cartilage deformation between the groups.

Specific Aim 2: To identify patient and clinician-oriented correlates of talar cartilage thickness (at rest) and deformation in those with CAI.

Research Questions

2.1.1 Pearson correlations will be run between self-reported function scores and talar cartilage thickness at rest in those with CAI.

2.1.2 Pearson correlations will be run between self-reported function scores and percentage Δ of talar cartilage thickness after a standing protocol in those with CAI.

2.1.3 Pearson correlations will be run between self-reported function scores and percentage Δ of talar cartilage thickness after a hopping protocol in those with CAI.

2.2.1. Pearson correlations will be run among distances during the weight-bearing lunge test, reach distances during star excursion balance test, and talar cartilage thickness at rest in those with CAI.

2.2.2. Pearson correlations will be run among distances during the weight-bearing lunge test, reach distances during star excursion balance test, and percentage Δ of talar cartilage thickness after a standing protocol in those with CAI.

2.2.3. Pearson correlations will be run among distances during the weight-bearing lunge test, reach distances during star excursion balance test, and percentage Δ of talar cartilage thickness after a hopping protocol in those with CAI.

2.3.1. Pearson correlations will be run between times and distances during functional hop tasks and percentage Δ of talar cartilage thickness after a standing protocol in those with CAI.

2.3.2. Pearson correlations will be run between times and distances during functional hop tasks and percentage Δ of talar cartilage thickness after a hopping protocol in those with CAI.

Specific Aim 3: To identify laboratory-oriented correlates (i.e. biomechanical and sensorimotor outcomes) of talar cartilage thickness (at rest) and deformation in those with CAI.

Research Questions

3.1.1. Pearson correlations will be run between AP and IE joint laxity and talar cartilage thickness at rest in those with CAI.

3.1.2. Pearson correlations will be run between AP and IE joint laxity and percentage Δ of talar cartilage thickness following a standing protocol in those with CAI.

3.1.2. Pearson correlations will be run between AP and IE joint laxity and percentage Δ of talar cartilage thickness following a hopping protocol in those with CAI.

3.2.1. Pearson correlations will be run among COP velocity and TTB mean in both AP and ML directions and talar cartilage thickness at rest in those with CAI.

3.2.2. Pearson correlations will be run among COP velocity and TTB mean in both AP and ML directions and percentage Δ of talar cartilage thickness after a standing protocol in those with CAI.

3.2.3. Pearson correlations will be run among COP velocity and TTB mean in both AP and ML directions and percentage Δ of talar cartilage thickness after a hopping protocol in those with CAI.

3.3.1. Pearson correlations will be run among ankle joint angles at initial contact during walking, hopping, and jump landing, and talar cartilage thickness at rest in those with CAI.

3.3.2. Pearson correlations will be run among ankle joint angular ranges while single limb standing and ankle joint angles at the initial contact during walking, and percentage Δ of talar cartilage thickness after a standing protocol in those with CAI.

3.3.3. Pearson correlations will be run among ankle joint angles at the initial contact during single limb standing and walking, and percentage Δ of talar cartilage thickness after a hopping protocol in those with CAI.

3.3.4. Pearson correlations will be run among peak vertical ground reaction forces and loading rate during the loading phase of single limb standing and walking, talar cartilage thickness at rest, and percentage Δ of talar cartilage thickness after a standing protocol in those with CAI.

3.3.5. Pearson correlations will be run among peak vertical ground reaction forces and loading rate during the loading phase of hopping and jump landing, and percentage Δ of talar cartilage thickness after a hopping protocol in those with CAI.

If a variable is not normally distributed, a Spearman correlation analysis will be used. For all aims, we will account for potential covariates (i.e. age, sex, time since an initial ankle sprain) if necessary. An alpha level of 0.05 will be used to determine statistical significance in all analyses. Hedge's G between group effect sizes and 95% confidence intervals based on the change scores will also be calculated and interpreted as follows: less than 0 as small, 0.31–0.7 as moderate, and greater than 0.71 as large. Finally, control condition data will be used to calculate the minimal detectable change (MDC) scores for all cartilage outcomes. The MDC allows us to evaluate the deformation values relative to the stability of the average thickness measures over time.

CHAPTER 4: GENERAL RESULTS

Specific Aim 1

To determine if talar cartilage deformation using ultrasonography following a standardized standing and hopping protocols differs between those with CAI and healthy controls.

Results

Prior to loading, no differences in cartilage thickness existed between assessment days or groups ($p>0.05$). For the dynamic loading condition, when controlling for weight, Group × Time interactions were observed for medial ($p=0.043$) and overall ($p=0.038$) talar cartilage thickness, indicating that the CAI group had greater talar cartilage deformation relative to the control group. There was also a Time main effect observed for lateral ($p=0.031$) cartilage thickness indicating that talar cartilage deformation increased after dynamic loading (Figure 4.1.1).

For the static loading protocol, Group × Time interactions were observed in overall ($p=0.032$) and medial ($p=0.006$) talar cartilage thickness when controlling for weight. Those with CAI had greater talar cartilage deformation compared to healthy individuals. However, there was no significant Time ($p=0.237$) or Group ($p=0.156$) effect for lateral cartilage when accounting for weight (Figure 4.2).

The raw change scores in overall cartilage thickness following both loading conditions exceeded the calculated MDC for each assessment day. Group means, standard deviations, raw changes, and MDCs can be seen in Table 4.1.1 and 4.1.2.

Figure 4.1.1. Talar cartilage thickness changes following a 60-hop protocol.

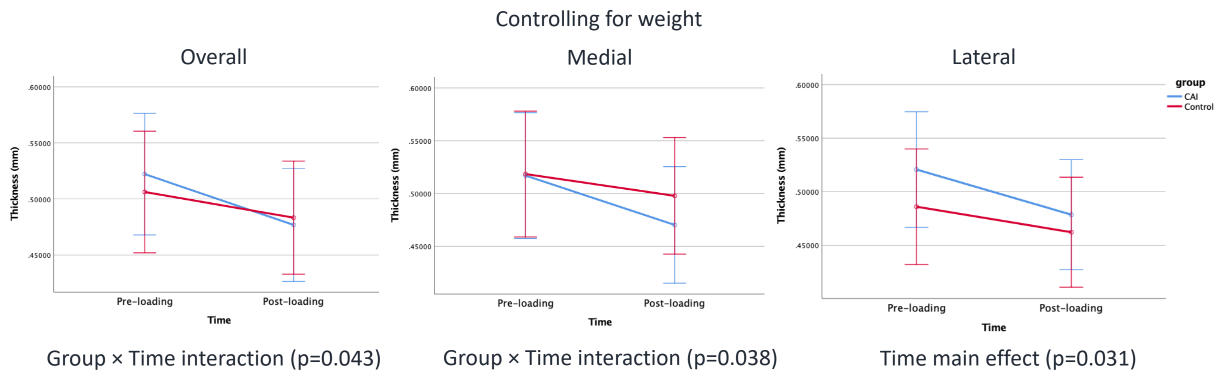


Figure 4.1.2. Talar cartilage thickness changes following a 2-min standing protocol.

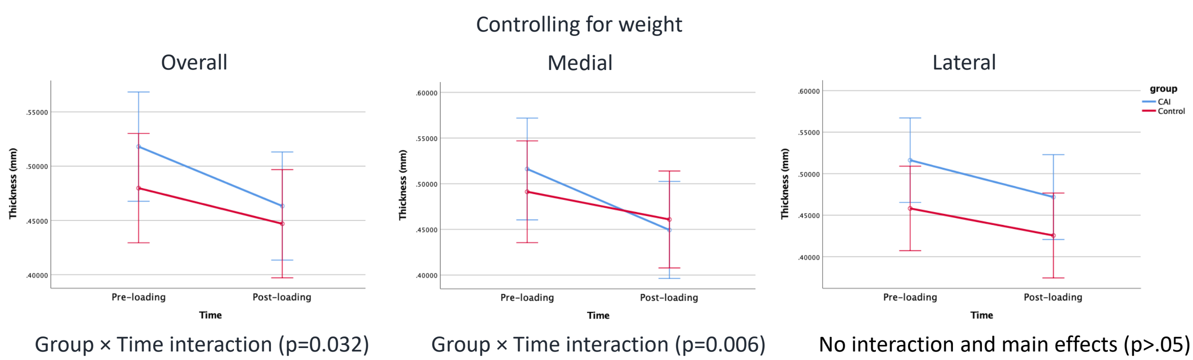


Table 4.1.1. Pre-post talar cartilage thickness changes following a 60-hop protocol.

	Group	Pre-loading (mm)	Post-loading (mm)	Raw change (mm)	MDC (mm)
Overall	CAI	0.54±0.17	0.49±0.15	-0.050±0.054	0.025
	Control	0.49±0.12	0.47±0.11	-0.018±0.021	0.017
Medial	CAI	0.53±0.18	0.48±0.15	-0.050±0.054	0.026
	Control	0.50±0.13	0.49±0.13	-0.017±0.036	0.019
Lateral	CAI	0.54±0.18	0.49±0.16	-0.048±0.063	0.034
	Control	0.47±0.12	0.45±0.11	-0.018±0.011	0.022

Table 4.1.2. Pre-post talar cartilage thickness changes following a 2-min standing protocol.

	Group	Pre-loading (mm)	Post-loading (mm)	Raw change (mm)	MDC (mm)
Overall	CAI	0.53±0.14	0.48±0.15	-0.054±0.038	0.014
	Control	0.47±0.13	0.43±0.12	-0.033±0.032	0.013
Medial	CAI	0.53±0.15	0.46±0.15	-0.066±0.046	0.030
	Control	0.48±0.14	0.45±0.13	-0.031±0.043	0.029
Lateral	CAI	0.53±0.15	0.48±0.16	-0.045±0.042	0.022
	Control	0.45±0.12	0.41±0.11	-0.032±0.045	0.018

Specific Aim 2

To identify patient and clinician-oriented correlates of talar cartilage thickness (at rest) and deformation in those with CAI.

Results

<u>2.1. Relationship between self-reported function score and talar cartilage thickness and deformation in those with CAI.</u>

Ankle Osteoarthritis Scale (AOS) and Foot and Ankle Outcome Score (FAOS)

Greater lateral deformation after static loading was correlated with greater FAOS symptom and stiffness (p=.031) and sport function (p=.049) subscales. No other associations were found (p>.05)

Table 4.2.1.1. Pearson correlation coefficients (*r*) between AOS and FAOS and cartilage thickness and deformation

	AOS		FAOS					
	Pain	Disability	Symptom & stiffness	Pain	ADL function	Sport function	Quality of life	Total
At rest								
Medial	-.095	-.304	-.141	-.044	-.007	-.102	-.185	-.106
Lateral	-.081	-.290	-.110	-.009	.051	-.144	-.186	-.074
Overall	-.090	-.300	-.126	-.027	.023	-.129	-.185	-.091
Static loading								
Medial	-.256	-.161	-.122	.155	-.087	-.145	-.109	-.051
Lateral	-.193	-.011	**-.402***	-.048	-.021	**-.369***	-.229	-.223
Overall	-.273	-.124	-.285	.080	-.050	-.275	-.165	-.136
Dynamic loading								
Medial	-.120	-.167	.086	.340	.239	.168	.123	.254
Lateral	.026	-.030	-.131	.197	.090	.061	.024	.074
Overall	-.052	-.108	-.028	.286	.169	.133	.081	.174

AOS: Ankle Osteoarthritis Scale, FAOS: Foot and Ankle Outcome Score, ADL: Activities of Daily Living
* indicates statistically significant correlations (p<.05).

SF-36 questionnaires

There were no significant correlations between SF-36 questionnaire scores and talar cartilage thickness at baseline or deformation after static and dynamic loading. (p>.05)

Table 4.2.1.2. Pearson correlation coefficients (*r*) between SF-36 scores and cartilage thickness and deformation

	SF-36							
	Physical function	Physical limitation	Emotional limitation	fatigue	Emotional wellbeing	Social function	pain	Global health
At rest								
Medial	-.065	-.015	.155	.021	.219	.172	-.044	.329
Lateral	-.096	.013	.089	.021	.182	.123	-.044	.321
Overall	-.081	-.002	.124	.024	.202	.147	-.045	.326
Static loading								
Medial	-.059	-.097	-.285	.098	.006	-.241	.222	.077
Lateral	-.132	-.135	.007	.179	.155	-.026	-.088	.019
Overall	.665	.509	.459	.345	.587	.513	.641	.691
Dynamic loading								
Medial	.234	.279	-.076	.110	.197	.124	.319	.132
Lateral	.262	.078	-.040	.153	.044	-.071	.095	.233
Overall	.163	.349	.727	.489	.533	.913	.247	.266

Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaires

Greater medial (p=.012) and overall (p=.019) deformation after dynamic loading was moderately associated with decreased physical function scores measured by the PROMIS physical function (20a) questionnaire. No other relationships were found (p>.05)

Table 4.2.1.3. Pearson correlation coefficients (*r*) between PROMIS scores and cartilage thickness and deformation

	PROMIS				
	GH-Physical	GH-Mental	PF_SF	PF-20a	APSRA-SF8a
At rest					
Medial	.119	.247	.068	.014	.080
Lateral	.171	.262	.073	-.018	.127
Overall	.148	.263	.067	-.007	.106
Static loading					
Medial	.140	.077	-.033	.120	-.220
Lateral	.048	.205	.117	.024	-.293
Overall	.130	.171	.074	.112	-.305
Dynamic loading					
Medial	.249	.123	.224	**.467***	.282
Lateral	.269	-.022	.261	.344	-.002
Overall	.299	.055	.256	**.441***	.148

PROMIS: Patient-Reported Outcomes Measurement Information System, GH: Global Health, PF: Physical Function, SF: Short-form, APSRA: Ability to Participate in Social Roles and Activities
* indicates statistically significant correlations (p<.05).

2.2. Relationship between DFROM, dynamic postural control, and cartilage thickness and deformation in those with CAI.

Decreased DFROM on the WBLT was significantly correlated with increased medial talar deformation ($p=.034$). There were no associations between the normalized distance in mSEBT and cartilage thickness and deformation ($p>.05$)

Table 4.2.2. Pearson correlation coefficients (r) between WBLT and SEBT scores and cartilage thickness and deformation

	WBLT	SEBT		
	DFROM	Anterior	Posteromedial	Posterolateral
At rest				
Medial	-.222	.003	.283	.047
Lateral	-.187	-.108	.346	.084
Overall	-.204	-.052	.327	.076
Static loading				
Medial	-.148	.006	.177	.119
Lateral	-.142	-.090	.072	.000
Overall	-.218	-.080	.107	.027
Dynamic loading				
Medial	**.402***	.251	.183	.229
Lateral	.137	.146	.030	.131
Overall	.294	.221	.116	.197

WBLT: Weight nearing lunge test, SEBT: Star excursion balance test
* indicates statistically significant correlations ($p<.05$).

2.3. Relationships between times and distances during functional hop tasks and cartilage thickness and deformation in those with CAI

Increased distance during single leg hop and crossover hop tests correlated with thicker talar cartilage at baseline. For static loading protocol, the side hop test and overall (p=.024), and medial (p=.016) deformation were associated. For dynamic loading protocol, the side hop test and overall (p=.001), medial (p=.004), and lateral (p=.002) deformation were associated. More specifically, as side hop test time increased (worse performance), cartilage deformation increased.

Table 4.2.3. Pearson correlation coefficients (*r*) between functional hop test scores and cartilage thickness and deformation

	Functional Hop Tests			
	Figure 8	Sing leg hop	Cross over hop	Side hop
At rest				
Medial	-.201	**.561***	**.383***	-.018
Lateral	-.161	**.480***	.339	.037
Overall	-.184	**.530***	**.368***	.010
Static loading				
Medial	.206	.146	.124	**-.442***
Lateral	.075	.212	.223	-.288
Overall	.149	.204	.206	**-.418***
Dynamic loading				
Medial	-.174	-.010	-.108	**-.524***
Lateral	-.240	.131	.142	**-.555***
Overall	-.224	.062	.018	**-.591***

* indicates statistically significant correlations (p<.05).

Specific Aim 3

To identify laboratory-oriented correlates (i.e. biomechanical and sensorimotor outcomes) of talar cartilage thickness (at rest) and deformation in those with CAI.

Results

3.1. Relationships between AP and IE joint laxity and talar cartilage thickness at rest and deformation in those with CAI

There is no association between ankle joint laxity and cartilage thickness at rest (p>.05). For the static loading protocol, increased inversion laxity was moderately correlated with increased overall (p=.022) and medial (p=.012) talar deformation. For the dynamic protocol, decreased eversion laxity was moderately correlated with increased medial cartilage deformation (p=.017).

Table 4.3.1. Pearson correlation coefficients (*r*) between ankle joint laxity and cartilage thickness and deformation

	Joint Laxity			
	Anterior	Posterior	Inversion	Eversion
At rest				
Medial	-.142	-.227	-.276	-.291
Lateral	-.232	-.316	-.296	-.303
Overall	-.192	-.277	-.290	-.302
Static loading				
Medial	.084	.011	**-.460***	.183
Lateral	.230	-.237	-.208	-.059
Overall	.160	-.147	**-.423***	.053
Dynamic loading				
Medial	.298	.089	.041	**.449***
Lateral	.250	.237	-.010	.194
Overall	.295	.185	.011	.352

* indicates statistically significant correlations (p<.05).

3.2. Relationship among static postural control and talar cartilage thickness at rest and cartilage deformation in those with CAI.

10-s single-limb balance with eyes open

Increased thickness of the medial cartilage, at baseline, was correlated with increased ML TTB mean (p=.046) and ML TTB SD (p=.007). Also, ML TTB SD was correlated with increased lateral and overall thickness at rest. More specifically, as postural control increased, cartilage thickness increased at rest. For static loading, the ML TTB mean was moderately associated with lateral (p=.015) and overall (p=.021) talar deformation. Similarly, ML TTB SD was moderately correlated with medial (p=.014), lateral (p=.007), and overall (p=.002) talar deformation. More specifically, as postural control decreased (i.e. TTB scores decreased), cartilage deformation increased. For dynamic loading, no associations were found (p>.05).

10-s single-limb balance with eyes closed

No associations between eyes closed TTB variables and cartilage thickness at rest or after static and dynamic loading (p>.05) were noted.

Table 4.3.2. Pearson correlation coefficients (*r*) between static postural control and cartilage thickness and deformation

	Eyes Open				Eyes Closed			
	TTBML Mean	TTBAP Mean	TTBML SD	TTBAP SD	TTBML Mean	TTBAP Mean	TTBML SD	TTBAP SD
At rest								
Medial	**.380***	.180	**.497***	.051	-.098	-.093	-.158	-.184
Lateral	.293	.078	**.461***	.054	.022	.029	-.125	-.088
Overall	.339	.134	**.485***	.061	-.034	-.027	-.144	-.134
Static loading								
Medial	.275	.122	**.457***	.185	-.267	-.125	-.315	-.087
Lateral	**.456***	.172	**.498***	.117	.086	-.059	.087	-.025
Overall	**.435***	.147	**.570***	.133	-.123	-.125	-.131	-.082
Dynamic loading								
Medial	.062	.172	.010	.152	-.272	-.073	-.349	.047
Lateral	.052	-.016	.041	-.053	-.221	.047	-.285	.092
Overall	.754	.699	.885	.821	.140	.975	.057	.677

TTB: Time-to-boundary, ML: Mediolateral, AP: Anteroposterior, SD: Standard deviation
* indicates statistically significant correlations (p<.05).

3.3. Relationship among kinematic and kinetics during standing, walking, hopping, and jump landing, and talar cartilage thickness at rest and deformation in those with CAI.

Standing

Increased sagittal total excursion (the sum of displacement) during a 20-s single leg stance was associated with greater medial (p=.043) and lateral (p=.028) deformation after static loading protocol. Similarly, increased sagittal range (maximum – minimum) was correlated with increased medial cartilage deformation after static loading protocol (p=.019) and dynamic loading protocol (p=.010).

Table 4.3.3.1. Pearson correlation coefficients (*r*) between standing kinematics and cartilage thickness and deformation

	20-s Single Limb Stance			
	Sagittal total excursion (°)	Frontal total excursion (°)	Sagittal range (°)	Frontal range (°)
At rest				
Medial	-.088	-.036	-.118	.122
Lateral	-.060	.012	-.093	.172
Overall	-.070	-.011	-.104	.155
Static loading				
Medial	**-.379***	-.085	**-.432***	-.134
Lateral	.230	-.296	-.159	-.023
Overall	**-.408***	-.164	-.273	-.068
Dynamic loading				
Medial	-.106	.124	**-.480****	-.153
Lateral	.006	.070	-.215	-.074
Overall	-.051	.109	-.379*	-.113

* indicates statistically significant correlations (p<.05).

Walking

Cartilage thickness at rest was not correlated with any walking variables (p>.05).

For static loading protocol, increased internal peak inversion moment was associated with increased lateral (p=.004) and overall (p=.009) talar cartilage deformation. For dynamic loading protocol, increased inversion at initial contact was correlated with overall cartilage deformation (p=.044). Similarly, increased peak inversion was correlated with decreased deformation of the medial (p=.379) and lateral (p=.385) talar dome. The internal peak inversion moment (p=.045) and internal rotation moment (p=.045) were also correlated with overall talar cartilage deformation after dynamic loading.

Table 4.3.3.2. Pearson correlation coefficients (*r*) between walking kinematics and kinetics and cartilage thickness and deformation

	Self-selected walking											
	Peak vGRF (BW)	Loading rate (BW/s)	Sagittal IC (°)	Peak DF (°)	Frontal plane IC (°)	Peak IN (°)	Horizontal plane IC (°)	Peak IR (°)	Peak PF MM (Nm/kg/m)	Peak IN MM Nm/kg/m)	Peak IR MM (Nm/kg/m)	Walking speed (m/s)
At rest												
Medial	.034	.077	-.066	-.007	-.110	-.142	-.132	-.136	-.009	-.177	-.008	.113
Lateral	.052	.002	-.030	.030	-.022	-.057	-.150	-.154	-.006	-.178	-.015	.022
Overall	.048	.039	-.051	.013	-.064	-.098	-.139	-.142	-.008	-.178	-.013	.068
Static loading												
Medial	.248	.277	.200	.188	.236	.194	.095	.118	-.217	-.253	-.294	.199
Lateral	.230	.284	.088	-.079	.278	.166	-.099	-.280	-.347	**-.515***	-.301	.017
Overall	.251	.325	.198	.067	.253	.156	-.040	-.138	-.333	**-.476***	-.355	.116
Dynamic loading												
Medial	.148	-.082	-.177	-.142	.364	**.379***	.060	.104	-.316	-.313	-.361	-.026
Lateral	.098	-.062	-.120	-.135	.351	.338	-.079	-.144	-.306	-.371	-.334	-.167
Overall	.143	-.076	-.154	-.140	**.383***	**.385***	.000	-.016	-.341	**-.382***	**-.382***	-.101

vGRF: Vertical ground reaction force, BW: Body weight, IC: Initial contact, DF: Dorsiflexion, IN: Inversion, IR: Internal rotation, MM: moment

* indicates statistically significant correlations (p<.05).

Single leg Hop

For kinematics, decreased peak DF was associated with increased medial cartilage deformation ($p=.045$). Increased plantar flexion at initial contact was correlated with increased overall ($p=.376$) and medial cartilage deformation ($p=.020$). For kinetics, increased peak vGRF was correlated with overall ($p=.011$) and medial cartilage deformation ($p=.019$). Increased loading rate was associated with increased overall ($p=.027$) and lateral cartilage deformation ($p=.012$).

Table 4.3.3.3. Pearson correlation coefficients (*r*) between hopping kinematics and kinetics and cartilage thickness and deformation

			Sagittal Plane Kinematics					
	Peak vGRF (BW)	Loading rate (BW/s)	Ankle IC (°)	Peak DF (°)	Knee IC (°)	Peak Knee Flexion (°)	Hip IC (°)	Peak Hip Flexion (°)
At rest								
Medial	.078	.013	.087	.068	-.064	-.102	-.115	-.167
Lateral	.003	.004	.050	.089	-.056	-.090	-.086	-.150
Overall	.043	.013	.065	.084	-.063	-.103	-.100	-.158
Static loading								
Medial	.189	.102	.179	.128	-.267	-.202	-.208	-.176
Lateral	-.030	-.183	.016	.041	-.048	.077	-.187	-.282
Overall	.137	-.001	.131	.124	-.173	-.088	-.208	-.248
Dynamic loading								
Medial	**-.440***	-.252	**-.437***	**-.382***	.273	.275	-.148	-.153
Lateral	-.190	**-.470***	-.267	-.175	.254	.194	-.056	-.106
Overall	-.348	**-.401***	**-.376***	-.305	.304	.261	-.116	-.148

vGRF: Vertical ground reaction force, BW: Body weight, IC: Initial contact, DF: Dorsiflexion
* indicates statistically significant correlations ($p<.05$).

Double Limb Jump Landing (Landing Error Scoring System)

Increased plantar flexion at initial contact was correlated with decreased lateral talar cartilage thickness at rest (p=.045). Also, decreased peak DF during a landing was correlated with decreased medial (p=.030) and overall (p=.021) cartilage deformation after static loading. There were no associations between cartilage deformation after dynamic loading and landing variables (p>.05)

Table 4.3.3.4. Pearson correlation coefficients (*r*) between landing kinematics and kinetics and cartilage thickness and deformation

			Sagittal Plane Kinematics					
	Peak vGRF (BW)	Loading rate (BW/s)	Ankle IC (°)	Peak DF (°)	Knee IC (°)	Peak Knee Flexion (°)	Hip IC (°)	Peak Hip Flexion (°)
At rest								
Medial	-.075	-.158	-.334	.174	.121	-.142	-.162	-.028
Lateral	-.174	-.256	**-.382***	.246	.131	-.149	-.121	-.007
Overall	-.125	-.208	-.361	.214	.123	-.149	-.141	-.016
Static loading								
Medial	.226	.148	.208	**.403***	-.102	-.098	-.170	-.196
Lateral	-.132	-.129	-.152	.257	.084	-.056	-.081	-.091
Overall	.046	.004	.024	**.428***	-.003	-.103	-.154	-.150
Dynamic loading								
Medial	-.024	.012	-.089	-.059	.320	-.046	-.115	-.177
Lateral	.157	.132	-.019	.091	.298	-.051	-.024	-.160
Overall	.064	.069	-.062	.022	.353	-.041	-.077	-.198

vGRF: Vertical ground reaction force, BW: Body weight, IC: Initial contact, DF: Dorsiflexion
* indicates statistically significant correlations (p<.05).

Plans for Secondary Research Analysis (SRA)

SRA1: To determine if femoral cartilage deformation using ultrasonography following a standardized standing and hopping protocols differs between those with CAI and healthy controls.

SRA2: To identify patient, clinician, and laboratory-oriented correlates to femoral cartilage thickness (at rest) and deformation in those with CAI.

SRA 3: To determine the time needed for talar and femoral cartilage to reach a resting state (i.e. fully recovery from real world activity).

SRA 4: To determine if cumulative external loading (average steps-per-day and minutes of moderate-to-vigorous physical activity) during a one-week monitoring period correlates to talar and femoral cartilage deformation.

SRA 5: To determine if cumulative external loading (average steps-per-day and minutes of moderate-to-vigorous physical activity) during a one-week monitoring period correlates to talar cartilage recovery during a 60-minute off-loading period.

CHAPTER 5: MANUSCRIPT 1

Acute Talar Cartilage Deformation Following Static and Dynamic Loading In Those With And Without Chronic Ankle Instability: A Ultrasonographic Study

Introduction

Lateral ankle sprains are the most common musculoskeletal injury associated with physical activity and athletic participation, accounting for approximately 60% of all injuries that occur during interscholastic and intercollegiate sports.[3, 4] Up to 75% of individuals who sprain their ankle subsequently develop chronic ankle instability (CAI), a condition characterized by life-long residual symptoms, recurrent injury, and decreased physical activity.[5-7] Further, as many as 78% of those with CAI develop ankle post-traumatic osteoarthritis (PTOA).[8, 9] No effective PTOA treatment exists, particularly once joint disease becomes severe. Thus, early detection of changes in cartilage health is important for slowing PTOA progression following ankle sprains.

A hallmark feature of PTOA is a decline in articular cartilage health[26] but the earliest deleterious changes in cartilage health involve alterations in cartilage composition (e.g. reduced proteoglycan density, collagen disorganization) without overt changes in cartilage morphology (e.g. thickness).[27] Using magnetic resonance (MR) imaging techniques, for example, young CAI patients displayed compositional declines relative to controls,[28, 175] but talar cartilage volume did not differ between the groups.[175] These compositional changes are theorized to alter the ability of the cartilage to respond to loading[30] as cartilage composition governs cartilage behavior.[32]

Articular cartilage deforms in response to mechanical loading and the type of loading influences the amount of deformation. For example, previous MR and fluoroscopic studies indicate that static single limb loading in healthy individuals produce significant talar cartilage deformation ranging from 7% to 15%,[33, 176] whereas dynamic loading conditions (single leg drop jump, single limb hopping) produce cartilage deformation in the range of 2% to 15%.[33, 129] However, it remains unknown how CAI influences the magnitude of cartilage deformation relative to uninjured healthy controls during both static and dynamic loading. Thus, quantifying how cartilage responds to loading in those with CAI relative to healthy individuals may inform the development of a sensitive marker for identifying early changes in cartilage health.

Unfortunately, quantifying early joint degeneration has been limited to MR techniques which are too costly and time intensive to be useful as a clinical screening tool for poor cartilage health. However, ultrasonography (US) is a valid and reliable technique to assess cartilage thickness and cross-sectional area at the knee.[35-37] Our data also showed that US talar cartilage normalized CSA was correlated with talar MR volume.[177] Thus, US may represent a viable alternative to MR, but it is unknown if US is sensitive to talar cartilage deformation following acute loading or if it would be sensitive to cartilage behavior differences between those with and without CAI.

Therefore, the purpose of this study was to determine if talar cartilage deformation measured via US following standardized standing and hopping loading protocols differs between those with CAI and healthy controls. The secondary aim was to determine if US measurement of cartilage deformation reflects viscoelasticity (i.e. different magnitude of deformation with different loading rates) between the standing and hopping protocols. We hypothesized that the CAI group would demonstrate greater talar cartilage deformation following a 2-minute standing protocol and a 60-hop protocol relative to healthy controls. We also hypothesized that static loading would result in greater cartilage deformation relative to dynamic loading.

Methods

Experimental Design

In this study, a mixed-model design was utilized to asses talar articular cartilage thickness before and after two different loading conditions and between those with and without CAI. Loading conditions were completed on different days separated by at least 1 week. Sessions were completed at the same of day (±2h) to control for diurnal variation in talar cartilage.[178, 179]

Participants

We recruited a total of 60 participants (30 CAI and 30 healthy individuals) between the age of 18 and 35 years. CAI was defined as those individuals who: (1) have sustained at least one lateral ankle sprain; (2) have experienced at least two episodes of giving way within the past 6-months; and (3) score of >11 on the Identification of functional ankle instability (IdFAI). These criteria are in agreement with the guidelines established by the International Ankle Consortium's position statement.[138] Self-reported function, as measured by the Foot and Ankle Ability Measure (FAAM) was assessed but not used as an inclusion criterion consistent with the recommendations of the International Ankle Consortium.[138] Those with bilateral CAI were allowed to participant and the limb with worse IdFAI scores was considered the involved limb. Healthy individuals were included if they had no history of ankle sprains and giving way episodes and score <11 on the IdFAI. For uninjured controls, the dominant limb was defined as the limb that the participant preferred to use for kicking a ball, and was matched to the CAI involved limb. Exclusion criteria for both groups included known vestibular and vision problems, acute lower extremity and head injuries (<3 months), chronic musculoskeletal conditions (e.g., symptoms of OA, ACL deficiency), and a history of ankle surgery to fix internal derangements.[138] Participants' self-reported level of physical activity over the past month was captured using NASA physical activity Scale.[180] All subjects provided written informed consent that was approved by the university's biomedical Institutional Review Board.

Data collection procedures

Off-loading period

Prior to the completion of each loading condition, all participants completed an off-loading period of 45 minutes to minimize the effect of preceding physical activity on the cartilage.[132] During this period, all participants sat on a padded plinth with their back against a wall while in a long-sit position before three US images of the talar cartilage (Pre45) were captured. Then, participants completed an additional 15 minutes of off-loading before another set of US images (Pre60) were captured (Figure 5.1). This additional time was used as a control condition in order to calculate minimal detectable change values for cartilage deformation.

Ultrasonographic image acquisition

US images of the talar cartilage were acquired using the Phillips Lumify tablet-based ultrasound unit (Amsterdam, Netherlands) with a 12-MHz linear probe. Participants were positioned with their back against a wall and their knee positioned to 90 degrees of flexion and their ankles in a foot flat position (~50 degrees of plantar flexion) (see Figure 5.2A).[141] The probe was placed transversely in line with the medial and lateral malleoli and rotated to maximize reflection of the articular cartilage surface. A tape measure was secured to the treatment table, and the distance between the wall and the posterior calcaneus was recorded to ensure consistent participant positioning across all time points.[131] A transparency grid placed over the screen ensured probe placement consistency across time.[131] Three images of talar cartilage at each time point were obtained using identical methodology. Post-loading assessments were completed within 3 min of completing the loading protocols.

Loading protocols

For the static loading condition, participants stepped off the table with their uninvolved limb. Participants then shifted their weight to the involved limb and stood on the involved limb for 2 minutes with the knee in approximately 20° of flexion while holding the uninvolved limb at approximately 45° of knee flexion and 30° of hip flexion.[33] During this protocol, participants were allowed to lightly touch an adjacent wall to maintain their balance as needed.

For the dynamic loading condition, participants were moved to an adjacent hallway in a chair to align themselves with the starting position of the hop loading protocol. The loading protocol consisted of a series of 60 single leg forward hops, with each hop being 60cm in distance.[129] Participants were allowed to briefly place their non-hop leg down to regain their balance as needed. At the completion of the 60th hop, participants were again wheeled back to the assessment table for the post-loading assessments. The order of the loading conditions was counterbalanced between participants.

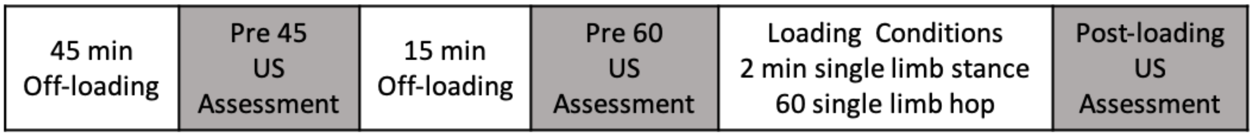


Figure 5.1. Study design. Each of the two data collection sessions were separated by at least 1 week. The loading conditions were counterbalanced for each participant.

Ultrasonographic image analysis

All US images were blinded such that the assessor was unaware of the timing (pre45, pre 60, post loading) of the image. However, the assessor was aware that a block of images was associated with a particular participant and were taken on a particular day. Talar cartilage images were manually segmented using ImageJ software (National Institutes of Health, Bethesda, MD, USA). The cartilage was initially segmented to identify the overall cross-sectional area (mm^2) by visualizing the entire visible cartilage area in the field of view. Medial and lateral cross-sectional area were then defined by splitting half the overall cartilage volume into medial and lateral portions of talar dome (see Figure 5.2B).[132] Finally, cross-sectional area of interest was normalized to the length of the cartilage-bone interface for the corresponding region to obtain an average thickness (mm). Average thickness from each of the three images taken at each time point were averaged and used for further analysis. Our preliminary data demonstrated excellent intra-rater reliability with this technique (ICC=0.93-0.97). In addition to the raw average thickness scores, percentage change scores were calculated for deformation using the following formula: Percentage change (%Δ) = $[(\text{mean}_{post} - \text{mean}_{pre60}) / (\text{mean}_{pre60})] * 100$.[132] A greater negative score indicates greater cartilage deformation.

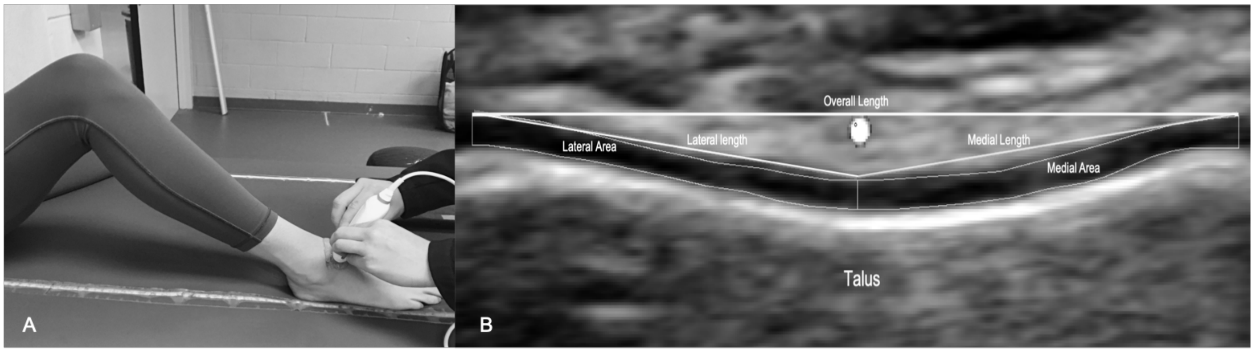


Figure 5.2. Ultrasonography image analysis. (A) positioning of participants and ultrasound transducer. (B) Cross-sectional area and length of each region of interest.

Statistical analysis

First, demographics were compared between CAI patients and healthy controls using independent sample t-tests. Next, we used 2-way (Group × Condition) univariate repeated measure analysis of variance (RMANOVA) to determine if pre-loading cartilage thickness measures (overall, medial, lateral) were similar between groups on each assessment day (i.e. hopping, standing). Next, cartilage deformation following the static loading protocol was assessed using three (overall, medial, lateral) separate 2-way (Group × Time) RMANOVA to determine if differences existed in cartilage deformation between the groups. An identical analytic approach was used to assess cartilage deformation following the dynamic loading protocol. Since weight was significantly different between groups, weight was entered as a covariate in each set of analyses. Control condition data (pre45 to pre60) was used to calculate the minimal detectable change (MDC) scores for all cartilage outcomes on each assessment day. MDC was calculated as: $1.645 \times \text{SEM} \times \sqrt{2}$ where standard error of measurement (SEM) = $\text{SD}\sqrt{1 - ICC}$.[131] The MDC allows us to evaluate if the deformation values exceeded measurement error.[131] To determine if the loading protocols resulted in different amounts of cartilage deformation, pre to post percent change scores for each condition, collapsed across groups, were calculated and compared using paired t-tests and bias corrected Hedge's g effect sizes with their corresponding 95% confidence intervals (95% CI). SPSS version 21.0 (SPSS Institute, Chicago, IL, USA) and an alpha level of 0.05 was used to determine statistical significance in all analyses.

Results

There was no significant difference between the groups in age ($p=0.462$) and height ($p=0.582$). Those with CAI weighed more ($p=0.013$), had a greater number of ankle sprains ($p<0.001$) and episodes of giving way within the past 6 months ($p<0.001$), higher IdFAI scores ($p<0.001$), and lower FAAM-ADL ($p<0.001$) and FAAM-S scores ($p<0.001$) compared to controls. Means and standard deviations for group demographics and injury characteristics can be found in Table 5.1.

Table 5.1. Participant demographics, injury history characteristics, and self-reported function.

	CAI (n=30)	Control (n=30)
Sex (Males, Females)	11, 19	7, 23
Age (years)	20.50±2.19	19.83±4.41
Height (cm)	171.49±6.65	170.89±8.63
Weight (kg)*	75.73±16.22	65.98±13.07
Identification of Functional Ankle Instability*	22.23±5.42	0.30±0.75
Foot & Ankle Ability Measure Activities of Daily Living subscale (%)*	87.39±10.97	99.92±0.30
Foot & Ankle Ability Measure Sport subscale (%)*	76.70±17.28	100±0
NASA PASS	6.03±2.09	6.37±2.22
Number of ankle sprains*	4.37±4.54	0±0
Number of giving way episodes within 6 months*	9.6±11.53	0±0

NASA PASS: National Aeronautics and Space Administration Physical Activity Status Scale.
* indicates statistically significant different between groups ($p<.05$).

There was no significant interaction between groups and conditions for pre-loading talar cartilage thickness [overall ($p=0.320$), medial ($p=0.211$), and lateral ($p=0.375$)]. There were also no significant Group ($p>0.215$) or Condition ($p>0.083$) main effects for pre-loading talar cartilage thickness, indicating there was no baseline difference between groups and conditions.

For the dynamic loading condition, when controlling for weight, Group × Time interactions were observed for medial ($p=0.043$) and overall ($p=0.038$) talar cartilage thickness, indicating that CAI the group had greater talar cartilage deformation relative to the control group. A Time main effect was observed for lateral ($p=0.031$) cartilage thickness, indicating lateral talar cartilage deformed after dynamic loading, but no differences in the magnitude of deformation between groups. (Figure 5.3) The raw changes in overall cartilage thickness following the dynamic loading exceeded the calculated MDC. Raw changes and MDCs can be seen in Table 5.2.

For the static loading protocol, Group × Time interactions were observed in overall ($p=0.032$) and medial ($p=0.006$) talar cartilage thickness when controlling for weight. Those with CAI had greater talar cartilage deformation compared to healthy individuals. No significant Time ($p=0.237$) or Group ($p=0.156$) main effects were observed for lateral cartilage when accounting for weight. (Figure 5.4) The raw changes in overall cartilage thickness following the static protocol exceeded the calculated MDC. Raw changes and MDCs can be seen in Table 5.2.

In the combined cohort, overall ($p=0.023$) and medial ($p=0.013$) cartilage deformation were greater following the static loading condition compared to the dynamic condition, but no difference in lateral ($p=0.183$) cartilage deformation was noted. Percentage change scores, p-values, and pre-to-post between group effect sizes for each group can be seen in Table 5.3.

Figure 5.3. Pre-post talar cartilage thickness changes following a 60-hop protocol.

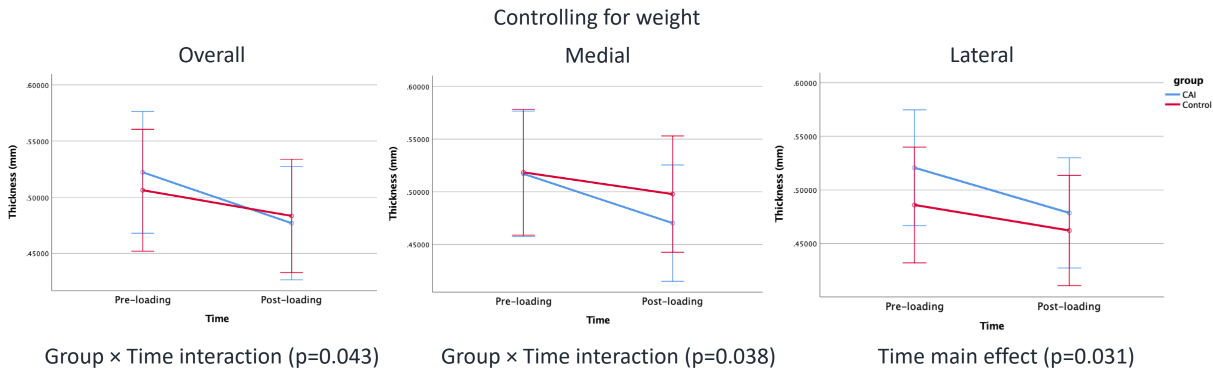


Figure 5.4. Pre-post talar cartilage thickness changes following a 2-min standing protocol.

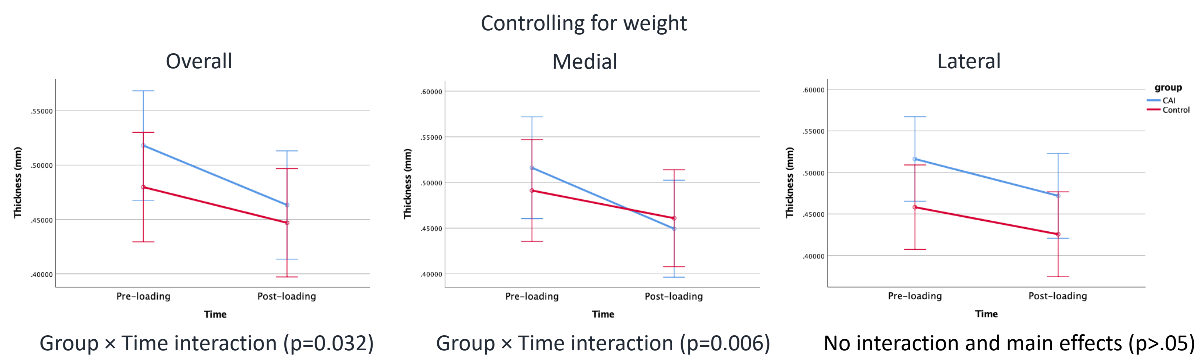


Table 5.2. Raw changes and minimal detectable changes (MDCs) for hopping and standing protocols.

	Group	Hopping Raw change (mm)	Hopping MDC (mm)	Standing Raw change (mm)	Standing MDC (mm)
Overall	CAI	-0.050±0.054	0.025	-0.054±0.038	0.014
	Control	-0.018±0.021	0.017	-0.033±0.032	0.013
Medial	CAI	-0.050±0.054	0.026	-0.066±0.046	0.030
	Control	-0.017±0.036	0.019	-0.031±0.043	0.029
Lateral	CAI	-0.048±0.063	0.034	-0.045±0.042	0.022
	Control	-0.018±0.011	0.022	-0.032±0.045	0.018

Table 5.3. Percentage changes after static and dynamic loading.

	Group	Hopping Percent change (%)	Standing Percent change (%)	p-value	Between Group Effect size (95% CI)
Overall	Combined	-6.03±7.38	-8.85±6.74	0.023	-0.39 (-0.90,0.12)
	CAI	-8.59±8.92	-10.87±6.96	0.207	-0.28 (-0.82,0.26)
	Control	-3.46±4.21	-6.84±5.98	0.054	-0.64 (-1.19,-0.10)
Medial	Combined	-5.91±8.28	-9.39±9.18	0.013	-0.39 (-0.90,0.12)
	CAI	-8.51±8.93	-12.98±8.16	0.019	-0.52 (-1.03,-0.01)
	Control	-3.31±6.80	-5.80±8.86	0.239	-0.31 (-0.85,0.23)
Lateral	Combined	-5.66±9.71	-7.90±8.32	0.183	-0.24 (-0.75,0.26)
	CAI	-8.10±10.92	-8.93±7.73	0.714	-0.09 (-0.62,0.45)
	Control	-3.20±7.77	-6.87±8.89	0.150	-0.43 (-0.97,0.11)

Discussion

US is a cost-effective and valid measure of ankle cartilage morphology[177] and acute cartilage deformation may provide a more functional measure of cartilage health than baseline morphology.[32] Our baseline US thickness did not differ between CAI and healthy individuals, and this result is consistent with previous studies using US thickness[181] and MRI volume[175]. Currently, there are limited data quantifying ankle cartilage deformation in response to physiological loading conditions in healthy individuals, but no studies have investigated this concept in those with CAI. The main finding of this study is that those with CAI have greater talar cartilage deformation in response to standardized static and dynamic loading relative to healthy individuals. Additionally, the absolute change in overall cartilage thickness following both conditions exceeded the MDC in both groups. These results support our a priori hypothesis and may be driven by declines in talar cartilage composition shown previously. Using MR, T2 mapping showed compositional changes (i.e. collagen disorganization) in young athletes who had functional ankle instability for <5 years.[28] Wikstrom et al. also found compositional declines (i.e. decreased proteoglycan density via T1rho MR scans) in college-aged CAI patients relative to controls.[175] Since composition drives cartilage behavior and those with CAI have worse composition, it is not surprising that CAI individuals have different cartilage behavior in response to a known physiologic load.[30]

To the best of our knowledge, this is first investigation to utilize US to quantify talar cartilage deformation in response to loading. As a result, we are only able to compare our results of cartilage deformation to MRI and fluoroscopy studies. Cher et al found, using MR, that the same hopping protocol resulted in a significant compressive strain of 2% in healthy individuals.[129] Our healthy individuals showed a similar amount of deformation (3.5%) while CAI individuals displayed greater deformation (8.6%). However, Van Ginckel et al. found that talar cartilage volume decreased 12.5% after 10 drop jump landings.[33] Thus, our percent deformation falls within the range reported in previous studies. Using an identical static protocol as the one used in our study, Van Ginckel et al. demonstrated a 14.6% cartilage deformation in healthy individuals.[33] Similarly, Wan et al. found a deformational strain of 7.5% over the entire tibiotalar contact area in healthy individuals.[176] Our healthy and CAI groups exhibited about 7% and 11% deformation after static loading, respectively. Although previous studies used different imaging methods, the magnitude of our US cartilage thickness deformation was within the range reported in the existing literature.

While both loading protocols produced measurable deformation in both groups, our results indicate greater talar cartilage deformation after static loading compared to dynamic loading. This difference may be explained by the biphasic theory.[182-184] During the dynamic loading condition, under higher forces and quicker loading, the deformational response of the extra-cellular matrix leads to higher hydraulic pressures allowing little deformation. On the other hand, the static loading condition allows interstitial fluids to gradually exude from the tissue by decreasing hydraulic pressure, which leads to greater deformation. Therefore, this result suggests that static loading may be a better stress test of cartilage behavior in those with CAI. However, further research needs to investigate a broader range of activities and the impact of cumulative loads on cartilage behavior in those with and without CAI.

A limitation of this study is that the US images could not capture the entire talar dome. Given current US imaging techniques and patient positioning, we are assuming that we captured the anterior superior portion of talar cartilage. Unfortunately, this means that we are unable to describe how static and dynamic loading affected the posterior talar cartilage. Additionally, we did not assess cartilage resiliency (i.e. recovery) after loading. Assessment of cartilage recovery following loading may also provide important information about cartilage health. Therefore, further research is needed to comprehensively evaluate cartilage deformation and resilience capacity and how this behavior associates with measures of composition in those with and without CAI.

Conclusion

In conclusion, this was first investigation to quantify acute talar cartilage deformation following known physiologic loads. At baseline, average thickness was comparable between the

CAI and control groups. However, a greater magnitude of talar cartilage deformation occurred after static and dynamic loading in those with CAI compared to healthy individuals. Our results suggest that US is capable to detecting differences in cartilage behavior between those with CAI and uninjured controls following standardized physiologic loads. Our results also demonstrate that static loading results in greater talar cartilage deformation compared to dynamic loading.

CHAPTER 6: MANUSCRIPT 2

In those with CAI, Functional Performance and Hop Biomechanics Associate with Greater Talar Cartilage Deformation Following a Dynamic Loading Protocol

Introduction

Lateral ankle sprains are one of the most common injuries sustained during athletic activities. [3, 4] About 40% of individuals with a previous history of ankle sprain suffer from a negative sequela of residual symptoms, recurrent ankle sprains, and/or feelings of instability long after the initial injury, a condition known as chronic ankle instability (CAI).[5-7] Further, up to 78% of patients with long term CAI develop ankle post-traumatic osteoarthritis (PTOA).[8, 9] Individuals who develop OA as a result of injury are estimated to be at least 10 years younger than individuals who develop primary ankle OA.[8] Further, the early onset of PTOA development results in decreased physical activity and quality of life as well as an increased public health burden.[48, 50] Unfortunately, there remain no effective conservative treatments for severe ankle OA, which further emphasizes the need to develop early intervention strategies to slow the progression of PTOA following lateral ankle sprains.

Healthy cartilage is supposed to deform in response to mechanical loading[31, 185] and several investigations have demonstrated this phenomenon in healthy individuals using MR.[33, 129] However, cartilage composition determines deformation response to acute mechanical loads[32, 186] and those with CAI have deleterious changes in talar cartilage composition.[175] A recent investigation using ultrasonography, demonstrated that those with CAI have greater talar cartilage deformation relative to uninjured controls following both static and dynamic loading conditions.[187] This altered cartilage response to loading has been theorized to play a role in further degeneration when coupled with abnormal forces.[188]

Understanding the factors associated with an altered deformation response may facilitate the development of early intervention strategies. It is theorized that both mechanical and sensorimotor impairments alter joint biomechanics and subsequently facilitate cartilage composition degradation (i.e. cartilage health).[55, 189] For example, passive[61, 190] and dynamic ankle dorsiflexion range of motion (DFROM)[15, 64] restrictions are present in those with CAI and worse DFROM is associated with poor landing biomechanics and increased vertical ground reaction force during single leg landing.[191] While many mechanical and sensorimotor outcomes are modifiable, no evidence currently exists to connect movement dysfunction with altered cartilage deformation patterns in response to a mechanical load. Elucidating such a link would provide insight regarding potential therapeutic targets to help slow ankle PTOA progression in those with CAI.

Therefore, the purpose of this study was to determine the relationship among DFROM, functional hop tests, and hopping biomechanics with talar cartilage deformation after a standardized dynamic (i.e. hopping) protocol. We hypothesized that decreased DFROM, worse functional hop test scores, and altered sagittal plane joint kinematics and kinetics during a single leg hop would be associated with increased talar cartilage deformation following a dynamic loading protocol.

Methods

Participants

30 CAI individuals (11 males and 19 females) participated in the study. Inclusion criteria for the consisted of being between 18-35 years of age, a history of at least one lateral ankle sprain, a history of at least two giving way episodes within the past 6 months, and scoring >11 on the Identification of functional ankle instability (IdFAI). Exclusion criteria included acute lower extremity and head injuries within 3 months, chronic musculoskeletal conditions (e.g. symptoms of OA, ACL deficiency), lower extremity fracture or surgery, and known vestibular and vision problems. These criteria are consistent with the guidelines established by the International Ankle Consortium's position statement.[138] If a participant reported bilateral CAI, the limb with worse IdFAI scores was used for testing. Participants' self-reported level of physical activity over the past month was captured using NASA physical activity Scale.[180] All participants provided written informed consent prior to participation, and the study was approved by the University's Institutional Review Board.

Procedures

Participants reported for two testing sessions that were separated by 1 week. During the first session, participants completed the weight-bearing-lunge test (WBLT), functional hop tests, and a biomechanical assessment of a single leg hop task. During the second session an ultrasonographic (US) assessment of talar cartilage health before and after a standardized dynamic loading protocol (i.e. hopping) was completed.

Dorsiflexion range of motion

Maximum weight-bearing ankle DFROM was assessed using the weight-bearing lunge test (WBLT).[157] This test requires participants to perform a modified lunge to determine the farthest distance the great toe can be from a wall (cm) when the ipsilateral knee can touch the wall without the heel lifting from the ground. Maximum lunge distance was recorded to the nearest 0.5cm. The WBLT is a reliable measure of dorsiflexion range of motion (ICC=0.80-0.99).[158]

Functional hop tests

Participants performed four different unilateral hopping tests that are commonly used to evaluate motor function in the clinical setting.[174] The hop tests include figure-8 hop, side-to-side hop, triple-crossover hop for distance, and single leg hop for distance.[174] The figure-8 test requires the named pattern over a 5-meter distance outlined by cones. Participants were instructed to hop as quickly as possible twice thorough the course on the involved limb. The side-to-side hop test requires 10, 30cm side to side single limb hops as quickly as possible. Both figure-8 and side-to-side hop tests were recorded to the nearest 10th of a second. The triple-crossover test requires 3 hops from a start line in a zigzag fashion, crossing over a line that is 15cm wide. The single-leg hop test requires a forward hop as far as possible. Both the triple-crossover and single-leg hop tests were recorded as the distance from the starting line to the heel position at the end of the jump. Each participant was instructed on how to perform the tests and allowed practice trials for each test until they felt comfortable with the testing procedures. Three test trials were recorded for each task and the best scores were used for analysis.[192] All participants were allowed 30 seconds of rest between trials and a 1-minute rest between tasks. The order of task completion was counterbalanced for each participant.

Lower extremity biomechanics

Hopping biomechanics were assessed using a 10-camera Vicon motion capture system (Oxford Metrics, Oxford, UK) synchronized with a force plate (Bertec Co, Columbus, Ohio, USA). Three-dimensional kinematics and kinetics were sampled at 120 and 1200Hz, respectively. All participants completed five trials of single leg hop task that covered a distance of 60 cm (24 inches) to the center of the force platform.[129] The participant started each trial by standing on the involved limb and hopped to the force plate. Three to five practice trials were allowed until participants felt comfortable with the task. A successful trial required the participant to land on the force plate and balance for 2 seconds.[129, 167, 168] Data were processed using Visual 3D (CMotion, Inc, Rockville, MD) to calculate both kinematic and kinetic variables. Markers and ground reaction forces (GRF) were low-pass filtered using a fourth-order, zero-lag, Butterworth filter with cutoff-frequencies of 10 Hz and 50 Hz, respectively. Kinematic variables included initial contact and peak joint angle of the ankle, knee, and hip in the sagittal plane. Initial contact was identified as the point in the trial when the vertical ground reaction force (vGRF) exceeded 20N. Kinetic variables included peak vGRF and loading rate, which were normalized to a participants' body weight. Peak vGRF was defined as the maximum vGRF data while loading rate was defined as the slope of the vGRF-time curve from initial contact to the impact peak.[163] The average of 5 data collection trials was used for further analyses.

Talar cartilage assessment

An assessment of talar cartilage cross sectional area was completed prior to the dynamic loading condition. Participants sat in a long-sit position for 60 minutes to unload the cartilage of the ankle.[34] Ultrasonographic images of the talar cartilage were acquired using the Phillips Lumify tablet-based ultrasound system (Amsterdam, Netherlands) with a 12-MHz linear probe. Participants were positioned with their back against a wall and their knee positioned to 90 degrees of flexion and their ankles in a foot flat position (~50 degrees of plantar flexion).[141] The probe was placed transversely in line with the medial and lateral malleolus and rotated to maximize reflection of the articular cartilage surface. A tape measure was secured to the treatment table, and the distance between the wall and the posterior calcaneus was recorded to ensure consistent participant positioning across all time points.[131] A transparency grid placed over the US screen ensured probe placement consistency across time.[131] Three images were obtained for pre-loading time point.

Next, participants were wheeled to an adjacent hallway to align themselves with the starting position of the hop loading protocol. The loading protocol consisted of a series of 60 single leg forward hops, with each hop being 60cm in distance.[129] Participants were instructed to avoid touching the ground with their non-involved limb but they were allowed to briefly place their non-involved leg down to regain their balance as needed. At the completion of the 60th hop, participants were again wheeled back to the assessment table to have three talar cartilage images taken in a manner identical to the pre-test. Post-loading assessments were completed within 3 min of completing the loading protocols.

To reduce bias, all US images were blinded such that the assessor was unaware of the timing (pre or post loading) of the image. Talar cartilage images were manually segmented using

ImageJ software (National Institutes of Health, Bethesda, MD, USA) to identify the overall, medial, and lateral cross-sectional area.[132] This was done by visualizing the entire cartilage area (overall) and then splitting the talar dome into medial and lateral portions by bisecting the visible artilage. Area was normalized to the length of the relevant cartilage-bone interface to estimate overall, medial, and lateral average thickness (mm). The three trial average thickness value at each time point were averaged and used for further analysis. Deformation was reported as a percent change score using the following formula: $\%\Delta = [(\text{mean}_{post} - \text{mean}_{pre}) / (\text{mean}_{pre})] * 100$.[132] A greater negative score indicates greater cartilage deformation.

Statistical analysis

All variables were tested for normality using Shapiro-Wilk tests (p=0.086-0.992). Descriptive statistics for demographics and all dependent variables were calculated. Pearson product moment correlations were used to evaluate the relationships between (1) WBLT and talar cartilage deformation, (2) functional hop test scores and talar cartilage deformation, and (3) hop biomechanics and talar cartilage deformation. SPSS version 21.0 (SPSS Institute, Chicago, IL, USA) and an alpha level of 0.05 was used to determine statistical significance in all analyses.

Results

Means and standard deviations for group demographics and injury characteristics can be found in Table 6.1. Descriptive statistics for all dependent variables are presented in Table 6.2. Decreased DFROM on the WBLT was significantly correlated with increased medial talar deformation (r=.402, p=.034) (Figure 6.1a). The side hop test associated with overall (r=-.591, p=.001), medial (r=-.524, p=.004), and lateral (r=-.555, p=.002) deformation. More specifically, as side hop test time increased (worse performance), cartilage deformation increased. No other significant correlations among functional tests were identified ($p>.05$).

For kinematics, decreased peak DF was associated with increased medial cartilage deformation ($r=-.382$, $p=.045$). Increased plantar flexion at initial contact was also correlated with increased overall ($r=.376$, $p=.376$) and medial cartilage deformation ($r=.437$, $p=.020$). Kinetically, increased peak vGRF was correlated with overall ($r=-.483$, $p=.011$) (Figure 6.1b) and medial cartilage deformation ($r=-.440$, $p=.019$). Similarly, an increased loading rate was associated with increased overall ($r=-.425$, $p=.027$) and lateral cartilage deformation ($r=-.470$, $p=.012$).

Table 6.1. Participant demographics, injury history characteristics, and self-reported function.

	CAI (n=30)
Sex (Males, Females)	11, 19
Age (years)	20.50±2.19
Height (cm)	171.49±6.65
Weight (kg)	75.73±16.22
Identification of Functional Ankle Instability	22.23±5.42
Foot & Ankle Ability Measure Activities of Daily Living subscale (%)	87.39±10.97
Foot & Ankle Ability Measure Sport subscale (%)	76.70±17.28
NASA PASS	6.03±2.09
Number of ankle sprains	4.37±4.54
Number of giving way episodes within 6 months	9.6±11.53

NASA PASS: National Aeronautics and Space Administration Physical Activity Status Scale

Table 6.2. Dependent Variable Descriptive Statistics.

Variable	Mean ± SD
Cartilage deformation (Percentage change)	
Medial (%)	-7.72 ± 8.61
Lateral (%)	-7.71 ± 9.23
Overall (%)	-7.34 ± 9.89
Dorsiflexion range of motion (cm)	8.48 ± 2.63
Functional hop tests	
Figure 8 hop (s)	14.05 ± 7.02
Single leg hop (cm)	123.21 ± 24.05
Cross-over hop (cm)	335.05 ± 75.53
Side-to-side hop (s)	10.83 ± 4.00
Single Leg Hop Biomechanics	
Initial contact angle[a]	
Ankle plantar flexion (degrees)	24.10 ± 8.21
Knee flexion (degrees)	4.01 ± 4.42
Hip flexion (degrees)	26.62 ± 6.76
Peak joint angle[a]	
Ankle Dorsiflexion (degrees)	-11.73 ± 4.04
Knee flexion (degrees)	41.49 ± 6.57
Hip flexion (degrees)	33.30 ± 9.65
Ground reaction forces	
Peak vertical ground reaction forces (body weight)	2.37 ± 0.18
Loading rate (body weight$\cdot s^{-1}$)	31.86 ± 5.46

[a] Positive values for kinematic variables indicate ankle plantar flexion, knee flexion, and hip flexion.

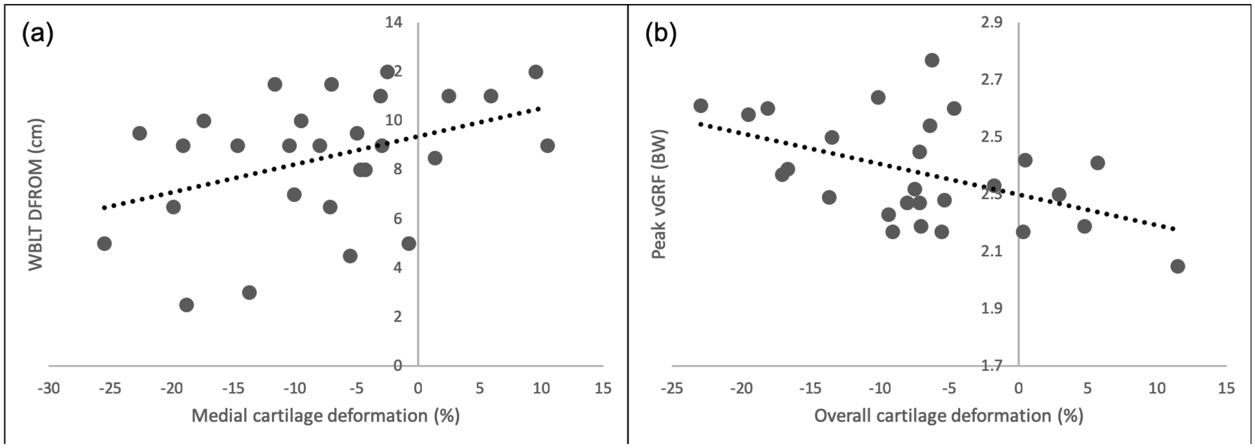


Figure 6.1. Scatter plot for (a) weight bearing lunge test and medial cartilage deformation and (b) peak vertical ground reaction force and overall cartilage deformation.

Discussion

The main finding of this study is that cartilage deformation magnitude correlates with weight-bearing DFROM measured using WBLT, side-to-side hop test, sagittal-plane kinematics, increased peak vGRF, and increased vGRF loading rate during a single leg hop task. These observations indicate that CAI related impairments influence talar cartilage behavior. If not treated, these impairments may have further negative consequences on cartilage health and for the development of degenerative changes within the ankle.

Cartilage deforms with mechanical loading and ankle cartilage deformation has been characterized after different loading exercises in healthy individuals.[33, 129, 176] Those with CAI have altered deformation behavior during static and dynamic loading conditions relative to uninjured controls.[187] The authors speculated that this altered behavior was due to compositional declines within talar cartilage following CAI.[28, 175] An inability to respond appropriately to loading has been hypothesized to predispose a joint to degenerative changes, particularly when abnormal high stresses are placed on the joint.[188] This physiological evidence further supports the need to elucidate potential therapeutic targets (i.e. factors that associated with altered deformation patterns) in those with CAI.

Mechanical insufficiencies and altered lower extremity biomechanics in those with CAI have been theorized to contribute to the development of ankle PTOA.[189] In healthy individuals, greater passive DFROM has been associated with less stiff landing strategies and decreased vGRF.[193] On the other hand, individuals with CAI commonly exhibit DFROM deficits compared to healthy individuals[15, 61, 190] and limited DFROM influences landing strategies.[15, 191] Thus, it is logical to hypothesize that limited static DFROM may also influence DFROM during a dynamic task. Our data support this relationship as DFROM measured via the WBLT correlates with peak DF during the hopping task ($r=0.707$, $p<0.001$). Also, statically and dynamically decreased DF was significantly correlated with increased talar deformation. Limited DFROM while landing likely contributes to an inability to attenuate forces muscularly and thus increases the stress on ankle joint cartilage.

Indeed, the associations between cartilage deformation and increased peak vGRF and vGRF loading rate would support this paradigm. Further, previous research shows greater peak vGRF and vGRF loading rate during running in those with CAI compared to healthy controls.[96] This increased impact force, over a shorter period of time, places the ankle under more stress,[194] which increases shear and rotational forces (i.e. increased contact strain) on the cartilage, and likely leads to degenerative changes.[8, 9, 20] For example, Bischof et al[21] found that the talar peak contact strain translated anteriorly and medially with increasing weight acceptance in the involved ankle of those with unilateral CAI. Bae et al[22] also found that talar cartilage strain was increased while walking in those with a history of ankle injury. Cumulatively, the literature has demonstrated altered biomechanical profiles in those with CAI and declines/alterations in cartilage health (e.g. increased strain, worse composition) in those with CAI. However, our results are the first to associate poor DFROM and poor kinetics with altered cartilage response patterns following a dynamic loading protocol.

Kinematically, we noted an increased plantar flexion angle at initial contact correlates with increased cartilage deformation. More plantar flexion position at initial contact may be better mechanical advantage at impact absorption via plantar flexors. However, previous researchers showed decreased strength[14], eccentric torque[73], and muscle inhibition[80, 81] of plantar flexors in those with CAI compared to healthy individuals. These could decrease ability to control impact forces and contribute to increase stress on the cartilage, which increasing cartilage deformation. However, further research should be conducted to confirm this speculation.

Only one clinician-oriented measure, the side hop test, was correlated with cartilage deformation magnitude. Functional hop tests assess multiple aspects of sensorimotor function. While speculative, sensorimotor dysfunction (e.g. poor postural control), commonly observed in those with CAI[12], may have altered participants movement patterns during the hop tasks and thus altered the load expressed on the ankle joint cartilage. While future research is needed, our results suggest the side hop test may be a viable clinical surrogate for talar cartilage behavior. The viability of a clinical measure is not without precedent as poor performance on a single-legged hop test early after anterior cruciate ligament injury was associated with the development of radiographic knee PTOA at 5 years after injury.[195]

This study provides insight into possible contributing factors of the development of degenerative changes associated with PTOA at the ankle. More specifically, intervention strategies to improve DFROM and reduce loading during a hop task may be helpful to minimize cartilage deformation after loading in those with CAI. Currently, joint mobilization techniques are used as effective tools for improving DFROM[196] and acutely increasing DF at initial contact during a single-leg drop landing in those with CAI.[197] Increased sagittal-plane joint displacement increases the duration of the loading phase, allowing enhanced force attenuation.[198, 199] However, future research is needed to directly quantify the short-term and long-term effect of these or other inventions on cartilage response to loading to further validate their potential as therapeutic targets that could minimize ankle joint degeneration.

This investigation is not without limitations. Given the ankle positioning with US procedures, we may be able to capture the anterior-superior talus. However, previous research showed that US talar cartilage image that was capture using the same technique was associated with overall talar dome in MR volume.[177] Another limitation is that multiple correlation tests and relatively small sample size may able to potentially increase in type I error. Therefore, it should be considered when interpreting the overall results.

Conclusion

In those with CAI altered ankle biomechanics and increased vGRF characterisitcs during a single leg hop were correlated with increased cartilage deformation after a dynamic loading protocol. Similarly, clinician-oriented measures such as decreased DFROM measured via the WBLT and worse performance on the side hop test were correlated with greater cartilage deformation in those with CAI. These results may provide a better understanding the factors contributing to altered cartilage behavior in response to a dynamic load in those with CAI and may represent targets for future therapeutic interventions.

CHAPTER 7: MANUSCRIPT 3

Ankle Joint Laxity and Postural Control Are Associated With Post Static Loading Cartilage Deformation In Those With Chronic Ankle Instability

Introduction

Ankle sprains are the most common injuries associated with physical activity and athletic participation,[4] accounting for approximately 60% of all injuries that occur during interscholastic and intercollegiate sports.[3, 4] Further, at least 1 out of every 3 individuals who sprains their ankle will go on to suffer chronic ankle instability (CAI); however, this number has been reported as high as 75%.[5, 6] Most importantly, CAI is a major contributing factor in the development of post-traumatic ankle osteoarthritis (PTOA)[52] for which there are no effective conservative treatments. Thus, the most promising approach for slowing PTOA progression are early interventions to address the underlying factors driving PTOA development in those with CAI.

A hallmark feature of ankle PTOA is a decline in articular cartilage health[26] which manifests initially as deleterious compositional changes (e.g. reduced proteoglycan density, collagen disorganization) in talar and/or subtalar cartilage in those with CAI.[175] Compositional changes are theorized to decrease the ability of the cartilage to appropriately respond to mechanical loading[30] since cartilage deformation is governed by cartilage composition.[32, 186] Talar cartilage deformation after loading in healthy individuals has been assessed via magnetic resonance (MR),[33, 129] but this method is difficult and expensive to quantify cartilage behavior. A recent investigation using ultrasonography (US), a more clinically scalable tool, demonstrated that those with CAI have altered deformation patterns relative to uninjured controls following static and dynamic loading conditions.[187]

Elucidating factors associated with altered cartilage behavior measured via US in those with CAI could provide clinicians with therapeutic targets to try and slow ankle PTOA progression. Current CAI paradigms theorize that structural adaptations (e.g. ligament laxity[13]) and sensorimotor dysfunction (e.g. postural control[82-84]) present in those with CAI facilitate altered biomechanics. Altered biomechanics subsequently alter ankle joint loading patterns and eventually initiates compositional declines.[189] Therefore, common impairments associated with CAI may play a role in determining how cartilage behaves following a mechanical load. Thus, the aim of this investigation was to identify potential associations between ankle joint laxity and single limb postural control measures with talar cartilage deformation after a standardized static (i.e. standing) loading protocol. We hypothesized that increased ankle joint laxity and worse postural control would be associated with increased talar cartilage deformation following a 2-min single limb stance.

Methods

Participants

30 CAI individuals (11 males and 19 females) between 18-35 years of age participated in the study. CAI was defined based on International Ankle Consortium guidelines: a history of ≥ 1 ankle sprain, ≥ 2 giving way episodes within the past 6-months, score ≥11 on the Identification functional ankle instrument (IdFAI).[138] Exclusion criteria included a history of (i) lower extremity surgery or fracture, (ii) balance and vision problems, (iii) acute (<12 weeks), and (iv) chronic musculoskeletal or head injuries/conditions. If a participant reported bilateral CAI, the

limb with a worse IdFAI score was used for testing. Self-reported function as measured by the Foot and Ankle Ability Measure (FAAM) was assessed but not used as an inclusion criterion. Also, self-reported level of physical activity over the past month was measured using NASA physical activity Scale.[180]

Procedures

Participants reported for two testing sessions that were separated by 1 week. During the first session, participants completed ankle joint laxity and standing postural control assessments. Participants then returned for the second session during which an US assessment of talar cartilage thickness before and after a standardized static loading protocol (i.e. standing) occurred. All participants provided written informed consent prior to participation, and the study was approved by the University's Institutional Review Board.

Ankle joint laxity assessment

An instrumented ankle arthrometer (Blue Bay Resarch Inc, Navarre, FL) was used to quantify the anterioposteror (AP) load-displacement and inversion-eversion rotational laxity characteristics of the involved ankle joint complex.[155] For AP displacement, the ankle was loaded with 125N of anterior and posterior force after starting in a neutral position. For rotational laxity, the ankle was loaded to 4Nm of torque in each direction. Three trials in each direction were averaged for further analysis.

Postural control assessment

Static and dynamic postural control were assessed using an AMTI force plate (AMTI; Watertown, MA) during single limb static stance. Subject performed three 10-s trials with their eyes open while standing on the involved limb with their hands on their hips that were averaged for further analysis.[172] Force plate data was collected at 50Hz and filtered using a fourth order, zero lag, low pass Butterworth filter with a cutoff frequency of 5Hz.[172] Then, time-to-boundary (TTB) means and standard deviations (SDs) in the AP and mediolateral (ML) directions were calculated using a custom MATlab code (MathWorks, Inc., Natick, MA, USA).[172] TTB is a spatiotemporal approach to assess how long individual has to make a postural correction to maintain balance.[172] Lower values indicate less time to make a postural correction and thus represent worse postural control. Dynamic postural control was assessed using the modified Star Excursion Balance Test (mSEBT) that consists of a series of lower-extremity reaching tasks in different directions.[200] Participants completed three trials of the anterior, posteromedial, and posterolateral mSEBT directions as previously reported.[173] Reach distances were normalized to the participant's leg length (i.e. anterior superior iliac spine to ipsilateral medial malleolus) before being used for further analysis.

Talar cartilage assessment

Talar cartilage thickness was assessed by calculating the cross-sectional area of a two-dimensional image. Participants sat in a long-sit position for 60 minutes prior to the pre-loading assessment to unload the ankle cartilage.[34] Ultrasonographic images of the talar cartilage were acquired using a Phillips Lumify tablet-based ultrasound unit (Amsterdam, Netherlands) with a 12-MHz linear probe. Participants were positioned with their back against a wall and their knee positioned to 90 degrees of flexion and their ankles in a foot flat position (~50 degrees of plantar flexion).[141] The probe was placed transversely in line with the medial and lateral malleolus and rotated to maximize reflection of the articular cartilage surface. A tape measure was secured to the treatment table, and the distance between the wall and the posterior calcaneus was recorded to ensure consistent participant positioning across all time points.[131] A transparency grid, placed over the US screen ensured probe placement consistency over time.[131] Three images of talar cartilage thickness were obtained at the pre-loading assessment time point.

Next, participants stepped off the table with their uninvolved limb. Participants then shifted their weight to the involved limb and stood on the involved limb for 2 minutes with the knee in approximately 20 degrees of flexion.[33] Participants were instructed to avoid touching the ground with their non-involved limb, but they were allowed to use their hands to briefly touch an adjacent wall to maintain balance as needed. At the completion of the loading protocol, participants sat back on the table and 3 more talar cartilage thickness images were taken using identical methodology. Post-test images were completed within 3 min of completing the loading protocol.

US Image analysis

To reduce bias, all US images were blinded such that the assessor was unaware of the timing (pre or post loading) of the image. Talar cartilage images were manually segmented using ImageJ software (National Institutes of Health, Bethesda, MD, USA) to identify the 1) overall, and 2) medial and lateral cross-sectional area of the talar cartilage.[132] This was done by visualizing the entire cartilage area and then splitting the cartilage into medial and lateral portions of talar dome by bisecting the overall area. Each cross-sectional area was normalized to the length of the cartilage-bone interface of the area in question to estimate average thickness (mm). Deformation was reported as a percent change in average thickness from pre to post loading using the following formula: $\%\Delta = [(\text{mean}_{post} - \text{mean}_{pre}) / (\text{mean}_{pre})] * 100$.[132] A greater negative score indicates greater cartilage deformation.

Statistical analysis

Descriptive statistics for demographics and all dependent variables were calculated. Pearson product moment correlations were used to evaluate the relationships between talar cartilage deformation and (1) ankle joint laxity a, (2) TTB outcomes during a single limb stance, and (3) mSEBT reach distances an. SPSS version 21.0 (SPSS Institute, Chicago, IL, USA) and an alpha level of 0.05 was used to determine statistical significance in all analyses. Pearson correlation coefficients (r) were interpreted as weak (0.00–0.40), moderate (0.41–0.69), or strong (0.70–1.00).[201]

Results

Means and standard deviations for group demographics and injury characteristics can be found in Table 7.1. Descriptive statistics for all dependent variables are presented in Table 7.2. For ankle joint laxity, greater inversion laxity was moderately correlated with greater overall and medial talar deformation (Figure 7.1a). For static postural control, the ML TTB mean was moderately associated with lateral and overall talar deformation (Figure 7.1b). Similarly, ML TTB SD was moderately correlated with medial, lateral, and overall talar deformation. More specifically, as postural control decreased (i.e. TTB scores decreased), cartilage deformation increased. For dynamic postural control, no significant correlations were identified. All correlations and p-values can be seen in Table 7.3.

Table 7.1. Participant demographics, injury history characteristics, and self-reported function.

	CAI (n=30)
Sex (Males, Females)	11, 19
Age (years)	20.50±2.19
Height (cm)	171.49±6.65
Weight (kg)	75.73±16.22
Identification of Functional Ankle Instability	22.23±5.42
Foot & Ankle Ability Measure Activities of Daily Living subscale (%)	87.39±10.97
Foot & Ankle Ability Measure Sport subscale (%)	76.70±17.28
NASA PASS	6.03±2.09
Number of ankle sprains	4.37±4.54
Number of giving way episodes within 6 months	9.6±11.53

NASA PASS: National Aeronautics and Space Administration Physical Activity Status Scale

Table 7.2. Dependent Variable Descriptive Statistics

Variables	Mean ± SD
Cartilage deformation (Percentage change)	
Medial (%)	-12.47 ± 7.94
Lateral (%)	-8.88 ± 7.44
Overall (%)	-10.61± 6.65
Ankle joint laxity	
Anterior (mm)	10.96 ± 2.68
Posterior (mm)	8.55 ± 2.12
Inversion (°)	32.03 ± 7.95
Eversion (°)	23.98 ± 10.48
Static postural control	
Mediolateral Time-to-boundary mean (s)	1.75 ± 0.53
Mediolateral Time-to-boundary standard deviation (s)	1.26 ± 0.43
Anteroposterior Time-to-boundary mean (s)	4.90 ± 1.18
Anteroposterior Time-to-boundary standard deviation (s)	3.21 ± 0.99
Dynamic postural control	
Anterior star excursion balance test (%leg length)	64.77 ± 6.57
Posteromedial star excursion balance test (%leg length)	78.74 ± 7.88
Posterolateral star excursion balance test (%leg length)	74.53 ± 9.46

Table 7.3. Pearson correlation coefficients (p-values) between ankle joint laxity and balance and cartilage deformation

	Ankle Joint laxity				Static single limb balance				SEBT		
	A	P	IN	EV	Mean TTBML	SD TTBML	Mean TTBAP	SD TTBAP	A	PM	PL
Medial	.084	.011	**-.460**	.183	.275	**.457**	.122	.185	.006	.177	.119
	(.665)	(955)	**(.012)**	(.343)	(.157)	**(.014)**	(.529)	(.336)	(.977)	(.359)	(.538)
Lateral	.230	-.237	-.208	-.059	**.456**	**.498**	.172	.117	-.090	.072	.000
	(.231)	(.216)	(.280)	(.763)	**(.015)**	**(.007)**	(.373)	(.545)	(.641)	(.709)	(.999)
Overall	.160	-.147	**-.423**	.053	**.435**	**.570**	.147	.133	-.080	.107	.027
	(.408)	(.446)	**(.022)**	(.785)	**(.021)**	**(.002)**	(.446)	(.491)	(.680)	(.579)	(.890)

A: anterior, P: posterior, IN: inversion, EV: eversion, TTB: time-to-boundary, ML: mediolateral, SD: standard deviation

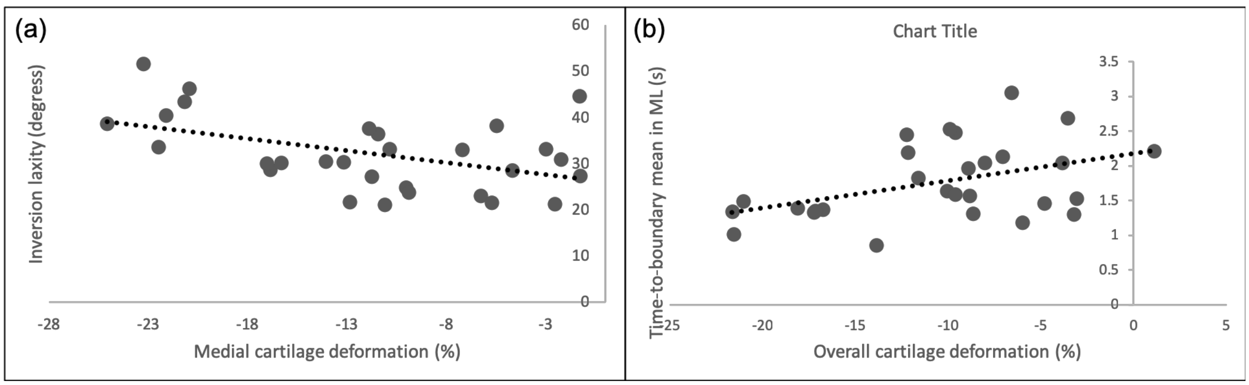


Figure 7.1. Scatter plots for (a) between inversion laxity and medial cartilage deformation and (b) time-to-boundary mean in mediolateral direction and overall cartilage deformation.

Discussion

The primary finding of our study was that the magnitude of cartilage deformation after a static loading protocol was correlated with greater inversion laxity and worse static postural control. These results partially support our a priori hypothesis. Our findings provide evidence that mechanical alterations and sensorimotor dysfunction commonly present in those with CAI partially explain how cartilage behaves following a static mechanical load.

Normal, healthy cartilage deforms predictably in response to physiological loading. When cartilage composition (i.e. type II collagen, proteoglycan) is disrupted, compressive stiffness is decreased and leads to a greater permeability to water, resulting in greater cartilage deformation.[117-119] Previous research demonstrated that a static load resulted in greater talar cartilage deformation than dynamic loading,[187] as consistent pressure would allow tissue to gradually exude interstitial fluids and decrease hydraulic pressures.

Mechanical joint instability occurs due to the damage of the lateral ligaments during ankle sprains, which lead to residual ankle joint laxity.[55] This increased joint laxity is thought to alter ankle joint kinematics and eventually result in cartilage degeneration.[21, 22, 54] For example, Lee et al.[53] found that ankles with a deficient anterior talofibular ligament had higher talar cartilage T2 values (worse composition) compared to an uninjured group.[21] Also, ankles with unilateral CAI showed an increased and anteromedially translated peak contact strain compared to contralateral healthy ankles during standing.[21] Previous research also demonstrates that individuals with CAI had an anterior talar position, relative to the tibia, and this positional fault may play a role in exerting load on portions of the talar dome not built to deal with such loads. Given the cumulative evidence, it is not surprising that our results help to converge these lines of research by illustrating a relationship between inversion laxity and an altered cartilage response pattern.

Our preliminary research showed that worse static postural control is associated with higher T1ρ value (worse cartilage composition) in those with CAI.[25] Similarly, our results showed that worse postural control particularly in the ML direction was correlated with greater talar cartilage deformation in response to loading. Although the exact mechanism is still unknown, sensorimotor system constraints after ankle sprains may lead to unbalanced loading of joint surfaces. While speculative, a greater ML COP change may result in a corresponding shift in cartilage strain away from the joint center. However, future research is needed to model joint loading during static postural control assessments to better understand the identified relationships.

No association was noted between mSEBT reach distances and cartilage deformation magnitude. Our result is consistent with previous research that indicated there was no relationship between mSEBT and T2-mapping (i.e. composition scores).[23] However, an association between longer ML time to stabilization, which is calculated from a single leg jump landing, and worse cartilage composition was noted in those with CAI.[23] These data may suggest that instrumented measures of dynamic postural control may be better indicators of cartilage behavior or that postural control measures based on force application (e.g. COP, TTS) are better indicators than a global measure of neuromuscular control (e.g. mSEBT).

The clinical implications of our study are that mechanical instability and decreased balance should be specifically targeted during rehabilitation protocols in an effort to improve cartilage behavior in response to static loading. Currently, external ankle supports (e.g. bracing, taping) are used as effective tools for preventing recurrent ankle sprains.[202] These tools are purported to provide mechanical stability to an unstable ankle joint but do not alter ankle kinematics.[203] Thus, it is unlikely that they would control/restore altered in vivo loading patterns within the ankle joint. However, lateral ligament reconstructions (e.g. Brostrom-Gould) decrease anterior translation and internal rotation of the talus under weight bearing loading when measured using MR and fluoroscopy.[204] While other conservative options should be investigated, the current evidence suggests that surgical reconstruction may be a good option to potentially restore factors that may play a part in ankle PTOA progression but future prospective research is needed to test this hypothesis. Balance training[205, 206] and manual therapy[207, 208] have been shown to improve static and dynamic postural control in those with CAI. Thus, these practices should be continued, but future research is needed to directly quantify the effect of these and other interventions that improve balance on cartilage health (i.e. composition and/or behavior following mechanical loads). Cumulatively, research is also needed to quantify the combined effect of surgical reconstruction and robust neuromuscular rehabilitation in those with CAI as no such data exists.

A possible limitation of our study was US is incapable of capturing the entire talar dome and we assume that we capture the anterior-superior talus. Another limitation is that we did not adjust the p-value for multiple correlation tests and relatively small sample size, which may increase in type I error. Therefore, it should be considered when interpreting the overall results.

Conclusion

Our data illustrates that greater inversion laxity and poorer static postural control are associated with greater talar cartilage deformation following a 2-minute static loading protocol. Given these relationships, it is recommended that mechanical instability and postural control be targeted during rehabilitation protocols in an effort to restore/improve cartilage behavior in response to mechanical loading. Further research is needed to determine how improving these impairments (instability and balance) improves cartilage behavior in those with CAI.

APPENDIX 1: IDENTIFICATION OF FUNCTIONAL ANKLE INSTABILITY

Appendix A. Final IdFAI

IDENTIFICATION OF FUNCTIONAL ANKLE INSTABILITY (IdFAI)

Instructions: This form will be used to categorize your ankle stability status. A separate form should be used for the right and left ankles. Please fill out the form completely and if you have any questions, please ask the administrator. Thank you for your participation.

Please carefully read the following statement:

"Giving way" is described as a temporary uncontrollable sensation of instability or rolling over of one's ankle.

I am completing this form for my **RIGHT/LEFT** ankle (circle one).

1.) Approximately how many times have you sprained your ankle? ________

2.) When was the last time you sprained your ankle?

❑Never ❑ > 2 years ❑ 1-2 years ❑ 6-12 months ❑ 1-6 months ❑< 1 month

3.) If you have seen an athletic trainer, physician, or healthcare provider how did he/she categorize your most serious ankle sprain?

❑Have **not** seen someone ❑Mild (Grade I) ❑Moderate (Grade II) ❑Severe (Grade III)

4.) If you have ever used crutches, or other device, due to an ankle sprain how long did you use it?

❑Never used a device ❑1-3 days ❑4-7 days ❑1-2 weeks ❑2-3 weeks ❑>3 weeks

5.) When was the last time you had ***"giving way"*** in your ankle?

❑Never ❑> 2 years ❑1-2 years ❑6-12 months ❑ 1-6 months ❑< 1 month

6.) How often does the ***"giving way"*** sensation occur in your ankle?

❑Never ❑Once a year ❑Once a month ❑Once a week ❑Once a day

7.) Typically when you start to roll over (or 'twist') on your ankle can you stop it?

❑Never rolled over ❑Immediately ❑Sometimes ❑Unable to stop it

8.) Following a typical incident of your ankle rolling over, how soon does it return to 'normal'?

❑Never rolled over ❑Immediately ❑ < 1 day ❑1-2 days ❑> 2 days

9.) During "Activities of daily life" how often does your ankle feel ***UNSTABLE***?

❑Never ❑Once a year ❑Once a month ❑Once a week ❑Once a day

10.) During "Sport/or recreational activities" how often does your ankle feel ***UNSTABLE***?

❑Never ❑Once a year ❑Once a month ❑Once a week ❑Once a day

APPENDIX 2: THE FOOT AND ANKLE ABILITY MEASRUES

Foot and Ankle Ability Measure (FAAM) – Activities of Daily Living Scale

Please answer every question with one response that most closely describes to your condition **within the past week**. If the activity in question is limited by something other than your foot or ankle mark not applicable (N/A).

	Side	No difficulty	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to do	N/A
Standing	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Walking on Even Ground	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Walking on even ground without shoes	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Walking up hills	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Walking down hills	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Going up stairs	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Going down stairs	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Walking on uneven ground	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Stepping up and down curbs	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Squatting	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Coming up on your toes	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Walking initially	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Walking 5 minutes or less	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
	Right	☐	☐	☐	☐	☐	☐

Walking approximately 10 minutes	Left	☐	☐	☐	☐	☐	☐
Walking 15 minutes or greater	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐

Because of your **foot and ankle** how much difficulty do you have with:

	Side	No difficulty	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to do	N/A
Home responsibilities	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Activities of daily living	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Personal Care	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Light to moderate work (standing, walking)	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Heavy work (push/pulling, climbing, carrying)	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Recreational activities	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐

How would you rate your current level of function during your usual activities of daily living from 0 to 100 with 100 being your level of function prior to your foot or ankle problem and 0 being the inability to perform any of your usual daily activities?

Right: .0 % Left: .0 %

FAAM Sports Scale

Because of your **foot and ankle** how much difficulty do you have with:

	Side	No difficulty	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to do	N/A
Running	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Jumping	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Landing	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Starting and stopping quickly	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Cutting/lateral movements	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Low impact activities	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Ability to perform activity with your normal technique	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐
Ability to participate in your desired sport as long as you would like	Right	☐	☐	☐	☐	☐	☐
	Left	☐	☐	☐	☐	☐	☐

How would you rate your current level of function during your sports related activities from 0 to 100 with 100 being your level of function prior to your foot or ankle problem and 0 being the inability to perform any of your usual daily activities?

Right: .0 % Left: .0 %

APPENDIX 3: THE INTERNATIONAL PHSYICAL ACTIVITY QUESTIONNAIRE

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE
The questions will ask you about the time you spent being physically active in the **last 7 days**. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

_____ **days per week** _____No vigorous physical activities

2. How much time did you usually spend doing **vigorous** activities on one of those days?

_____ **hours per day** _____ **minutes per day** _____Don't know/Not sure

Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

_____ **days per week** _____No moderate physical activities

4. How much time did you usually spend doing **moderate** activities on one of those days?

_____ **hours per day** _____ **minutes per day** _____Don't know/Not sure

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time? This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

_____ **days per week** _____No walking

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day** _____ **minutes per day** _____Don't know/Not sure

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**? . Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

_____ **hours per day** _____ **minutes per day** _____Don't know/Not sure

APPENDIX 4: THE FOOT AND ANKLE OUTCOME SCORE

FAOS FOOT & ANKLE SURVEY

Todays date: _____/______/______ Date of birth: _____/______/______

Name: ____

INSTRUCTIONS: This survey asks for your view about your foot/ankle. This information will help us keep track of how you feel about your foot/ankle and how well you are able to do your usual activities.
Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms
These questions should be answered thinking of your foot/ankle symptoms during the **last week**.

S1. Do you have swelling in your foot/ankle?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S2. Do you feel grinding, hear clicking or any other type of noise when your foot/ankle moves?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S3. Does your foot/ankle catch or hang up when moving?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S4. Can you straighten your foot/ankle fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

S5. Can you bend your foot/ankle fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

Stiffness
The following questions concern the amount of joint stiffness you have experienced during the **last week** in your foot/ankle. Stiffness is a sensation of restriction or slowness in the ease with which you move your joints.

S6. How severe is your foot/ankle stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

S7. How severe is your foot/ankle stiffness after sitting, lying or resting **later in the day**?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Pain

P1. How often do you experience foot/ankle pain?

Never	Monthly	Weekly	Daily	Always
☐	☐	☐	☐	☐

What amount of foot/ankle pain have you experienced the **last week** during the following activities?

P2. Twisting/pivoting on your foot/ankle

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P3. Straightening foot/ankle fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P4. Bending foot/ankle fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P5. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P6. Going up or down stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P7. At night while in bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P8. Sitting or lying

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P9. Standing upright

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your foot/ankle.

A1. Descending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A2. Ascending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your foot/ankle.

A3. Rising from sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A4. Standing

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A5. Bending to floor/pick up an object

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A6. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A7. Getting in/out of car

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A8. Going shopping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A9. Putting on socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A10. Rising from bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A11. Taking off socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A12. Lying in bed (turning over, maintaining foot/ankle position)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A13. Getting in/out of bath

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A14. Sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A15. Getting on/off toilet

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your foot/ankle.

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A17. Light domestic duties (cooking, dusting, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your foot/ankle.

SP1. Squatting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP2. Running

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP3. Jumping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP4. Twisting/pivoting on your injured foot/ankle

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP5. Kneeling

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Quality of Life

Q1. How often are you aware of your foot/ankle problem?

Never	Monthly	Weekly	Daily	Constantly
☐	☐	☐	☐	☐

Q2. Have you modified your life style to avoid potentially damaging activities to your foot/ankle?

Not at all	Mildly	Moderatly	Severely	Totally
☐	☐	☐	☐	☐

Q3. How much are you troubled with lack of confidence in your foot/ankle?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

Q4. In general, how much difficulty do you have with your foot/ankle?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Thank you very much for completing all the questions in this questionnaire.

Questionnaire and User's Guide can be downloaded from: www.koos.nu

APPENDIX 5: THE SHORT FORM-36

SF-36 QUESTIONNAIRE

Name:___________________ **Ref. Dr:__________________** **Date: _______**

ID#: ______________ **Age: _______** **Gender: M / F**

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:
In general, would you say your health is:
Excellent Very Good Good Fair Poor

Compared to one year ago, how would you rate your health in general now?
Much better now than one year ago
Somewhat better now than one year ago
About the same
Somewhat worse now than one year ago
Much worse than one year ago

LIMITATIONS OF ACTIVITIES:
The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
Yes, Limited a lot Yes, Limited a Little No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Lifting or carrying groceries
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Climbing several flights of stairs
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Climbing one flight of stairs
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Bending, kneeling, or stooping
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Walking more than a mile
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Walking several blocks
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Walking one block
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

Bathing or dressing yourself
Yes, Limited a Lot   Yes, Limited a Little   No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities
Yes   No

Accomplished less than you would like
Yes   No

Were limited in the kind of work or other activities
Yes   No

Had difficulty performing the work or other activities (for example, it took extra effort)
Yes   No

EMOTIONAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities
Yes   No

Accomplished less than you would like
Yes   No

Didn't do work or other activities as carefully as usual
Yes   No

SOCIAL ACTIVITIES:
Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all   Slightly   Moderately   Severe   Very Severe

PAIN:
How much bodily pain have you had during the past 4 weeks?

None   Very Mild   Mild   Moderate   Severe   Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all   A little bit   Moderately   Quite a bit   Extremely

Have you felt downhearted and blue?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel worn out?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a happy person?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel tired?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

SOCIAL ACTIVITIES:
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- All of the time
- Most of the time
- Some of the time
- A little bit of the time
- None of the Time

ENERGY AND EMOTIONS:
These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a very nervous person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt so down in the dumps that nothing could cheer you up?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt calm and peaceful?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you have a lot of energy?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

GENERAL HEALTH:
How true or false is each of the following statements for you?

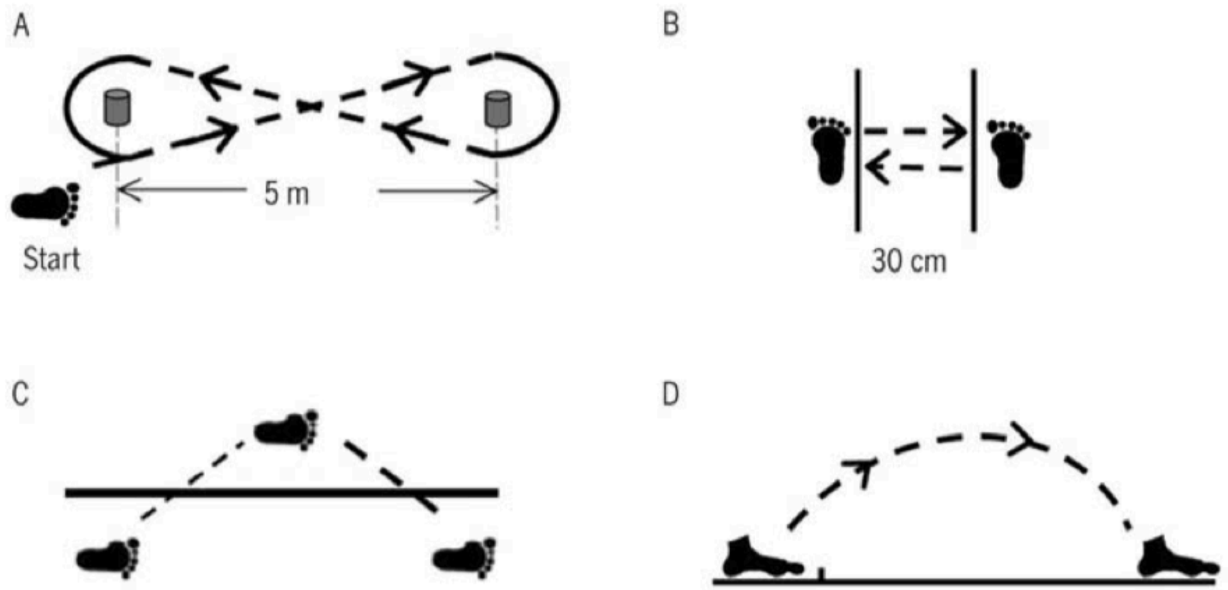
I seem to get sick a little easier than other people
◯ Definitely true ◯ Mostly true ◯ Don't know ◯ Mostly false ◯ Definitely false

I am as healthy as anybody I know
◯ Definitely true ◯ Mostly true ◯ Don't know ◯ Mostly false ◯ Definitely false

I expect my health to get worse
◯ Definitely true ◯ Mostly true ◯ Don't know ◯ Mostly false ◯ Definitely false

My health is excellent
◯ Definitely true ◯ Mostly true ◯ Don't know ◯ Mostly false ◯ Definitely false

APPENDIX 6: FUNCTIONAL HOP TESTS



APPENDIX 7: DATA COLLECTION SHEET

Number:__________________ Date:_______________

DOB:________ Height:___________ Weight:___________ Sex: _______

Dominant limb: _____ Involved limb: ______

Data collection time: Session1: Session2: Session3:

Ligament laxity

Involved limb	1	2	3
AP			
ML			

Weight Bearing Lunge Test

	1	2	3
Involved limb			

Navicular drop test

	1	2	3
Resting (cm)			
Weighted (cm)			

Rear-foot standing alignment

	1	2	3
Prone			
Weight			
SL stand			

SEBT

	1	2	3
Anterior			
PM			
PL			

Leg Length (PSIS to medial malleolus): __________

Functional testing

	Figure 8	Single leg hop	Cross-over hop	Side hop
1				
2				
3				

Biomechanics

20s single limb standing

	Standing
1	
2	
3	
4	
5	

Walking

	Practice	Trials
1		
2		
3		
4		
5		

Average	95%	105%

Hopping

	Hopping
1	
2	
3	
4	
5	

Jump landing (50% of height)

	LESS
1	
2	
3	
4	
5	

Single Limb Balance

-X, +X	-Y, +Y

eyes open

	1	2	3
Involved limb			

eyes closed

	1	2	3
Involved limb			

US measures

Positioning

Degrees (140)	Distance
Ankle	
Knee	

Hopping protocol
60 Single leg hops (Control1H001)

	0			15			30			45			60			Post		
Ankle	1	2	3	7	8	9	13	14	15	19	20	21	25	26	27	31	32	33
Knee	4	5	6	10	11	12	16	17	18	22	23	24	28	29	30	34	35	36

Standing protocol
2-minute single leg standing (20 degrees knee flexion) (Control1S001)

	0			15			30			45			60			Post		
Ankle	1	2	3	7	8	9	13	14	15	19	20	21	25	26	27	31	32	33
Knee	4	5	6	10	11	12	16	17	18	22	23	24	28	29	30	34	35	36

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